Response: Federal criteria will be implemented in accordance with existing state adopted compliance schedules. For a detailed discussion of this subject see a response to comment in subsection 4 of this section.

133. *Comment:* A commenter asserted that EPA did not do enough to educate the State early on of the 303(c)(2)(B) requirements and that EPA's final 303(c)(2)(B) guidance was not transmitted to the States until December 12, 1988, almost two years after the 1987 amendments. This delay left California with inadequate time to adopt criteria on a pollutant-by-pollutant and water body-specific basis, and consider the scientific uncertainties relating to the Federal data and methodologies.

Response: As stated in the Preamble to the proposed rule, the December, 1988 guidance was not substantially different from earlier drafts which were available for review by the states. That guidance proposed a pollutant-by pollutant and waterbody specific approach as an acceptable option. While recommending certain approaches, the guidance also made it clear that States retained flexibility to implement their own preferred approaches. Please see Science and Timing and Process under general comments.

134. *Comment:* One commenter stated that Region IX's requirement that California adopt criteria for all priority pollutants is erroneously based on statements in California's Functional Equivalent Documents and is inconsistent with national guidance. Another commenter stated that this requirement was unfounded.

Response: Region IX has consistently advised California that it must adopt criteria for all pollutants for which EPA has section 304(a) criteria recommendations, with the exception of any pollutants which cannot reasonably be expected to interfere with designated uses. Omission of any such pollutant must be based on evidence concerning the presence and effect of that pollutant in any given waterbody. This policy is consistent with national guidance, the history of which is set forth in Part B2 of the Preamble of November 19, 1991. None of the guidance options has ever allowed the exclusion of any such pollutant from the requirements of section 303(c)(2)(B) without a factual scientific basis. In the absence of such scientific basis, EPA relied on California's draft Functional Equivalent Document which stated that "it is likely that priority pollutants not covered in this plan will be found [in the State] in a more extensive analytical survey." This statement is sufficient basis for EPA to have determined that all priority pollutants would reasonably be expected to interfere with designated uses in all waters of the State.

135. *Comment:* The Federal criteria are more stringent than necessary for some water bodies in California.

Response: Without specific information about which pollutants and which water bodies the commenter is referencing, EPA has difficulty responding to this comment. In the absence of such specific information, EPA determined that it was appropriate to adopt EPA's section 304(a) criteria for all "waters of the U.S." that lack State-adopted, EPA-approved criteria. If, based on further scientific information, the State adopts site-specific criteria which are less stringent than the Federal criteria but, in EPA's judgment, fully meet the requirements of the Act, EPA will undertake a rulemaking to remove the affected pollutants from the Federal rule. For additional information, please see Science under general comments.

136. *Comment:* Major wastewater dischargers in California have filed a petition in State court to restrain the State from utilizing its section 303(c)(2)(B) standards for inland waters, bays, and estuaries. They filed the petition out of concern over significant economic impacts caused by blanket imposition of the [EPA] criteria. The filing of the petition illustrates the concerns of many public agencies over use of EPA criteria as national standards.

Response: The petition referred to in this comment is a challenge to section 304(a) criteria which have been adopted by the State. It is a pending proceeding in State court and does not affect today's rulemaking. The commenter states that this matter reflects a widespread concern over adoption of section 304(a) criteria as national standards. That concern is apparent in the comments received from several entities, particularly in California, and they are addressed in the Economics under general comments.

137. *Comment:* A commenter stated that "only marine criteria should be selected for enclosed bays in California since these are, by definition, indentations along the coast which enclose an area of oceanic water. It is not appropriate to apply freshwater criteria to these water bodies." The commenter also indicated that States should be given the discretion to determine when freshwater or salt water criteria should apply in an estuary.

Response: State standards in California's Inland Surface Waters and Enclosed Bays and Estuaries Plans have been approved for most of the priority toxic pollutants. These standards include both freshwater and saltwater uses and leave the selection of appropriate criteria to the regional boards. EPA approved the two sets of criteria on November 6, 1991. The Federal rule has been amended to reflect this approval. The final Federal rule applies to those parameters and also to water bodies where State standards are lacking or not protective. The regional boards shall determine for both State and Federal criteria whether freshwater or saltwater criteria are appropriate at the confluence of the water bodies with different water quality objectives.

District of Columbia

138. *Comment:* The adequacy of new human health criteria has not been proven to be germane to the District of Columbia.

Response: As a general proposition, EPA is applying criteria for all priority toxic pollutants not addressed by approved State criteria for those States not in full compliance with section 303(c) of CWA. EPA's reasoning behind this approach (and the exceptions) are discussed fully in the preamble. However, two reasons deserve repeating here. First, existing data sources indicate the discharge, potential discharge or presence of substantial numbers of priority toxic pollutants in most States. With the failure of some States to adopt toxic criteria in a timely fashion, coupled with the evidence of the discharge or potential presence of priority toxic pollutants for which the State has failed to adopt criteria, the Agency believes there is a need for numeric criteria for most priority toxic pollutants in most States. Second, the support of each criterion on a state-by-state and waterbody-by-waterbody basis by EPA would be an enormous administrative burden on EPA and would be contrary to the statutory scheme and Congressional directive for swift action. Congress directed EPA to accomplish the promulgation within 90 days and EPA has made every effort to expedite this rulemaking. Providing the adequacy for all criteria for all States would take years and would be counter to the directive of swift action.

Florida

139. *Comment:* One commenter stated that, since the State of Florida adopted numeric criteria on December 7, 1990 based on Option II of EPA's section 303(c)(2)(B) guidance, the Federal rule should not include criteria for all priority toxic pollutants.

Response: Since the time that the proposed rulemaking was published, Florida formally requested EPA's review of the criteria adopted by the State on

December 7, 1990. EPA approved these criteria, with the exception of the absence of criteria for 2,3,7,8 TCDD (i.e., dioxin) on February 25, 1992. Therefore, EPA has only included criteria for 2,3,7,8 TCDD for the State of Florida in the final rulemaking.

Kentucky

140. *Comment:* One commenter stated that Kentucky has proposed and adopted a revision to 401 KAR 5:031 which deletes the previously adopted numeric human health criteria for dioxin. A request was made by the commenter that EPA's determination of full compliance for Kentucky for the section 303(c)(2)(B) requirement be considered and a Federal water quality criteria be promulgated through this Federal rulemaking. Alternatively, a request was made that such criteria be established as an interim final rule in a separate rulemaking.

Response: At the time EPA published the proposed rulemaking, the State-adopted criteria for 2,3,7,8, TCDD for the State of Kentucky was in effect as part of 401 KAR 5:031 (Surface water standards). EPA is aware that the proposed deletion of 2,3,7,8 TCDD criteria was put into effect on January 29, 1992. EPA's position on Kentucky's proposed deletion of the State-adopted dioxin criteria was transmitted to Kentucky by letter dated November 21, 1991. In that letter, EPA's Region IV Water Management Division Director stated, "Should the State complete adoption of the proposed amendment without replacing the adopted dioxin criteria with approvable criteria values, I will recommend to the Regional Administrator that the dioxin criteria, or absence of dioxin criteria, be disapproved by EPA. If the State does not adopt criteria within 90 days of EPA's disapproval action, EPA will initiate a promulgation of Federal water quality criteria for dioxin for the State." This continues to be EPA's position on this issue.

Louisiana

141. *Comment:* EPA should not promulgate dioxin standards for Louisiana.

Response: Louisiana submitted to EPA criteria to protect human health for dioxin on December 18, 1991. EPA's review found that the criteria adopted by the State were scientifically defensible and supported the designated uses. EPA approved the State standard on January 24, 1992. Therefore, Louisiana is not included in today's rule.

Nevada

142. *Comment:* A Nevada commenter suggested that Column D1 criteria should apply only at the point of intake of any municipal or domestic supply.

Response: Column D1 criteria are to apply to all waters designated by the State of Nevada for municipal or domestic supply. In the case of Lake Mead, that is the entire lake except for the segment at the end of Las Vegas Bay recognizing that Las Vegas Wash enters there. All of Lake Mead is subject to human consumption of water either directly from the lake or downstream.

143. *Comment:* It was stated that the State of Nevada has already considered and rejected criteria similar to the proposed amendments, and Nevada's decision is not contrary to the requirements of the Clean Water Act.

Response: The State excluded criteria similar to those in the proposed rulemaking from the water quality standard amendments considered for adoption by the Nevada State Environmental Commission (SEC). The State did not provide an adequate justification for this exclusion; therefore, on January 16, 1991, EPA disapproved this portion of the SEC action as being inconsistent with section 303(c)(2)(B). Without substantive justification (such as evidence of lack of presence of particular pollutants in waters of the State) for excluding any of the priority pollutants from State standards, all of them must be added.

144. *Comment:* A Nevada commenter stated that Las Vegas Wash should be excluded from any human health protection for consumption of aquatic organisms under the Federal rule.

Response: The general issue of the applicability of column D2 (consumption of aquatic organisms) criteria is discussed in the preamble and in the Science portion of general comments. Human health protection is required where a fishery, or other aquatic life that can be consumed, is present. Las Vegas Wash has been designed by the State for the use of "Propagation of aquatic life, excluding fish." State regulations clarify that this designation does not preclude the establishment of a fishery. Although the commenter offers anecdotal information that no one fishes in (or eats any kind of aquatic organism from) Las Vegas Wash, no evidence is provided supporting that anecdotal information. No use attainability analysis has been conducted to justify removal or amendment of this use. Also, the State has already adopted (and EPA approved) standards for protection of aquatic life in Las Vegas Wash. Because of the existing aquatic life use and the potential for consumption of aquatic organisms, EPA has applied column D2 criteria to Las Vegas Wash.

145. *Comment:* A Nevada commenter stated that the proposed rule does not provide sufficient notice as to why certain criteria were included and others excluded from the proposed rulemaking for Nevada.

Response: The rulemaking includes criteria only for parameters that Nevada did not adopt, or, if the State did adopt criteria for a parameter, for parameters that were specifically disapproved. This information was all part of the administrative record associated with Nevada's adoption of numeric standards for toxics in May 1990 and EPA's approval/disapproval on January 16, 1991 and was available to the public prior to the notice of EPA's proposed rule, and during the public comment period for the proposed rule.

New Jersey

146. *Comment:* A commenter argues that New Jersey is in compliance with section 303(c)(2)(B) of the Clean Water Act because the State incorporates section 304(a) criteria, by reference, in their Water Quality Standards Regulation for actions involving the development of water quality based effluent limitations for point sources.

Response: While the State Water Quality Standards Regulation does incorporate section 304(a) criteria by reference, the standards do not specify the application factors necessary to implement criteria (e.g., a risk level for carcinogens). Further, the reference in the water quality standards regulation limits application of these criteria to actions involving the development of water quality-based controls for point sources while water quality standards must serve as the basis for controls on all sources, point and nonpoint.

147. *Comment:* A commenter noted that water quality criteria were not proposed in the promulgation for New Jersey waters classified as PL (Pinelands), or as mainstem Delaware River and Delaware Bay (zones 1C-6).

Response: EPA agrees that, due to EPA oversight, criteria were not proposed in the promulgation for New Jersey waters classified as PL (Pinelands) or as mainstem Delaware River and Delaware Bay (zones 1C-6).

Appropriate criteria for New Jersey waters classified as PL (Pinelands), and as mainstem Delaware River and Delaware Bay (zones 1C-6) are now included in this final rule.

Puerto Rico

148. *Comment:* A commenter stated that EPA's proposed rule presents serious problems regarding its implementation, specifically in determining the waters to which such criteria would be applicable in the Commonwealth of Puerto Rico.

Response: The Puerto Rico Water Quality Standards Regulations is clear regarding the designated uses of all waters of the Commonwealth of Puerto Rico. EPA is assigning necessary and appropriate criteria to support those uses in order to satisfy the requirements of section 303(c)(2)(B) of the Clean Water Act.

149. *Comment:* A commenter stated that the Puerto Rico Water Quality Standards Regulation, which establishes the classifications and designated uses, does not comply with the Federal Water Quality Standards Regulation in terms of the adoption of subcategories of uses, the need to conduct use attainability analyses when standards are exceeded, the adoption of a variety of uses for a single waterbody, and in considering the social and economic needs of the Commonwealth.

Response: While the Federal Water Quality Standards Regulation authorizes the adoption of subcategories of uses, States are not required to adopt subcategories of uses in the establishment of standards. States are not required to complete use attainability analyses (UAAs) when designated uses are not met. Section 131.10(j) of the water quality standards regulation requires that States must complete UAAs when removing designated uses that are not existing uses, or when specifying uses inconsistent with the goals of the Clean Water Act. States may not remove designated uses if they are existing uses. In the establishment of water quality standards and water body classifications, including requisite public participation, Puerto Rico has taken social and economic needs of the Commonwealth into consideration, as well as the inherent differences in levels of protection and water quality required by the various designated uses. Notwithstanding this discussion, the rule only addresses appropriate criteria for priority toxic pollutants. Other elements of State water quality standards are not addressed.

150. *Comment:* It was commented that the Puerto Rico Water Quality Standards Regulation does not recognize the uses of waterbodies that are actually attained.

Response: Designated uses of waterbodies are not required to only reflect those uses that are actually attained. While the Puerto Rico Water Quality Standards Regulation defines Class SD waters as surface waters intended for use as a raw water source for public water supply and the preservation and propagation of desirable species, not all Class SD waters presently meet these goals. Designated uses need not be existing uses. Consolidation of various uses (i.e., fishing and swimming) into one classification is an acceptable approach for designating uses of waterbodies, and a necessary one in order to meet the goal of the Clean Water Act. Federal regulations require that waters have designated uses that provide for fishable/swimmable water quality where attainable. When establishing criteria to protect these various designated uses, criteria may be specified to protect each use.

Washington

151. *Comment:* The term "water supplies" should be deleted from the Class AA listing in (22)(i) because it is incorrect.

Response: EPA concurs, it was a misprint.

152. *Comment:* Comments were received that EPA should not promulgate criteria for dioxin in the State of Washington. The commenters expressed concerns that EPA's actions would be disruptive and unnecessarily interfere with ongoing State administrative and judicial actions involving Department of Ecology's decisions in establishing effluent limitations in permits issued to numerous pulp and paper mills. The Department of Ecology had established the permit effluent limitations based on the State's existing narrative water quality criterion. The commenters urged EPA to defer action pending the conclusion of the ongoing State actions challenging the State's authority to establish permit limitations based on its narrative criterion. In addition commenters said that the current State regulations met the requirements of section 303(c)(2)(B) and that the State's regulations were equivalent to another State's water quality standards that an EPA region had approved as being in compliance with section 303(c)(2)(B).

Response: EPA carefully considered the comments on this issue and has decided to exercise its discretionary authority under section 303(c)(4)(B) to promulgate human health criteria for dioxin and the other toxic pollutants to be applicable to waters in the State of Washington. This action will ensure that there are numeric water quality criteria applicable in the State as required by section 303(c)(2)(B).

EPA's review of the current Washington water quality standards for toxic pollutants indicates that those standards do not include the necessary water quality criteria to satisfy the requirements of section 303(c)(2)(B). While WAC 173-201-047(1) includes numeric aquatic life criteria, protection of human health is only addressed through a narrative criterion that provides that toxic substances not be introduced at levels which "adversely affect public health, as determined by the department * * *." WAC 173-201-047(4). EPA believes that this limited narrative criterion does not satisfy the requirements of section 303(c)(2)(B).

EPA acknowledges that the Department of Ecology relied upon its narrative criterion to establish effluent limitations for dioxin in State NPDES permits. EPA supported the Department's reliance in its narrative criterion in developing necessary effluent limitations for the control of discharge of dioxin. EPA encourages all States to have narrative criteria for protection of aquatic life, wildlife and human health in instances when the State does not have an applicable numeric criterion. However, section 303(c)(2)(B) is clear in its directive that States adopt numeric criteria for toxic pollutants if EPA has issued section 304(a) guidance and the discharge or presence of such pollutants could reasonably be expected to interfere with designated uses in the State.

In the notice of proposed rulemaking, EPA discussed the basis for its decision to include Washington in the rule. 56 FR at 58477. The absence of any numeric criteria for human health and the acknowledged discharge and presence of toxic pollutants being expected to interfere with designated used supported inclusion of Washington in the rule. With respect to dioxin, the issuance of permits with discharge limitations was further evidence that the discharge or presence of dioxin could reasonably be expected to interfere with designated basis.

EPA does not believe that promulgation of numeric criteria for the State of Washington should be delayed pending resolution of the ongoing litigation challenging the Department of Ecology's authority to establish effluent limitations based on the State's narrative criterion. The State's narrative criterion, while it may be the basis for deriving effluent limitations, is not adequate to satisfy the requirements of Section 303(c)(2)(B). Some commenters argued that Washington had in effect incorporated by reference EPA's Section 304(a) water quality criteria guidance as the basis for interpreting and

implementing the State's narrative criterion. The Washington water quality standards, however, merely provide that for toxic substances not listed in the standards, concentrations shall be determined "in consideration of USEPA's Quality Criteria for Water, 1986, and as revised, and other relevant information." WAC 173–201–047(3). The State standards neither require use of EPA's criteria nor limit the State's decision to use of such criteria. Therefore, even a decision by the Washington Supreme Court that the Department of Ecology is authorized to use its narrative criterion to develop permit effluent limitations would not address the specific requirement of section 303(c)(2)(B) that the State adopt numeric criteria.

In response to the comments that the current Washington regulations are equivalent to regulations adopted by the Commonwealth of Massachusetts which is not included in today's rulemaking, EPA believes there is a important difference between the two State regulations. The Massachusetts regulations provide that in deriving criteria for unlisted pollutants, the State "shall use the recommended limit published by EPA pursuant to section 304(a) * * *." Code of Massachusetts Regulations, Title 314, section 4.05(5)(e). Pursuant to an Implementation Policy adopted on February 23, 1990, Massachusetts stated that it would use a risk management goal of 10^{-6} for individual chemicals and 10^{-5} for mixtures of chemicals in deriving criteria for carcinogens. The regulations contain a specificity regarding what the applicable criteria will be that is not present in the Washington regulations. EPA's Region I determined that the Massachusetts regulations complied with section 303(c)(2)(B) and approved those regulations on December 20, 1990. See 56 FR 58452.

EPA's decision to promulgate appropriate human health criteria for the State of Washington is consistent with the Agency's prior statements regarding the status of Washington's compliance with Section 303(c)(2)(B). In the Federal Register notice of April 17, 1990, EPA identified Washington as not being in compliance with section 303(c)(2)(B). 55 FR 14350. By letter dated March 27, 1990, from the Department of Ecology to EPA, the Department listed the adoption of human health criteria as an action for its triennial review that had been requested by EPA. By letter dated March 21, 1991, from EPA to the Department of Ecology, EPA explained that the State would remain in noncompliance under section 303(c)(2)(B) for human health criteria even if the State proceeded to adopt aquatic life criteria and a human health risk level. These documents are in the record of this rulemaking.

Executive Order 12291

1. Introduction and Rationale for Estimating Costs

Executive Order 12291 requires EPA to prepare a Regulatory Impact Analysis for major regulations, which are defined by certain levels of costs or impacts. For example, the Executive Order specifies that a regulation imposing an annual cost to the economy of $100 million or more is considered major. According to the Executive Order, the Regulatory Impact Analysis should contain descriptions of both potential costs and benefits. While the Executive Order calls for an estimate of costs, the Statute mandating today's rule does not allow cost to be a consideration in setting water quality criteria. The following discussion describes the Agency's consideration of costs in the rulemaking and decision process even though cost considerations are not included in the development of numeric criteria for toxic pollutants.

In developing the proposed rule, EPA considered various perspectives regarding the potential incremental costs that might be incurred as a result of the Agency promulgating numeric criteria for individual States. The Agency concluded that the costs incurred by individual dischargers as a result of complying with water quality-based permits might be large enough to designate the rule as "major," according to the definitions included in Executive Order 12291. The Agency did not include a quantitative estimate of the costs due to the uncertainties of such an estimate, but instead, described the types of costs that were expected.

There are certain characteristics of the rule that make the estimation of costs particularly complicated and difficult. Since the rule imposes requirements only until the State submits, and EPA approves, the State's own numeric standards, the cost estimates should be calculated on a per State and per pollutant basis, so that State/pollutant combinations can be removed as numeric standards are approved. Additionally, an analysis of the incremental costs attributed to the rule should reflect information on specific impaired stream segments and the dischargers on those segments.

Because a detailed analysis of all affected stream segments is not practical given the available resources, the development of compliance cost estimates for this rule would require numerous assumptions about pollutant loadings, impacts of technology-based regulations on loadings, combinations of pollutants handled by a given treatment approach, and the costs of each treatment train. The many sources of uncertainty associated with estimating the costs would produce an estimate with limited value for evaluating the merits of the rule. In addition, the rule does not remove the responsibility of States to adopt numeric criteria for toxic pollutants. As the remaining States submit their own standards and EPA approves those standards, the costs attributed to the rule will decline. Hence, EPA, with the concurrence of OMB, proceeded with the proposed rulemaking without a quantitative estimate of compliance costs.

2. Overview of Projected Costs

EPA acknowledges that there will be a cost to some dischargers for complying with new water quality standards as those standards are translated into specific NPDES permit limits. The addition of Federally promulgated criteria for toxic pollutants could affect the wasteload allocations developed for each waterbody segment in affected States to the extent the pollutant is discharged into the stream. Revised wasteload allocations may result in adjustments to individual NPDES permit limits for point source dischargers, and these adjustments could result in increased wastewater treatment costs or other pollution control activities such as recycling or process changes. The magnitude of these costs depends on the types of treatment or other pollution control, the number and type of pollutants being treated, and the level of control that can be achieved by technology-based effluent limits for each industry.

Similar sources of costs and the variables affecting costs may also apply to indirect industrial dischargers to the extent that the industrial discharger is a source of toxic pollutants discharged by the POTW. The POTW may incur costs for expansion, operational changes, additional treatment, modified pretreatment programs, and increased operator training.

Nonpoint sources of toxic pollutants may also incur increased costs to the extent that best management practices need to be modified or applied to more sources to reflect the revised water quality standards. Although there is no Federal permit program for nonpoint sources comparable to that for point sources, there are State regulatory programs to control nonpoint source discharges.

Monitoring programs are another source of potential incremental costs to dischargers and States. Monitoring programs to generate information on the existing quality of water and the types and amount of pollutants being discharged are potentially affected by the imposition of EPA criteria. The addition of Federal criteria for toxic pollutants does not require the State to engage in a program to monitor ambient waters for such pollutants. Unless there is some reasonable expectation that the pollutants are manufactured or actually used in the State with the likelihood that those pollutants will be discharged into surface waters, NPDES permittees also would not have to monitor for these pollutants.

3. Comments and EPA's Response

EPA received numerous comments regarding the potential cost impacts of the rule; most of these comments contend that a Regulatory Impact Analysis is required. Specifically, many commenters asserted that EPA should estimate the costs that dischargers would incur and include such cost estimates in all decision-making aspects of the rule. Some of these comments argued the qualitative discussion of costs did not fulfill the requirements of E.O. 12291.

EPA does not concede that its rationale for *not* estimating costs was flawed. Rather than appear nonresponsive, however, the Agency recognizes that further discussion is warranted and has undertaken an assessment of potential costs that might be incurred for several types of dischargers.

This cost assessment is not a Regulatory Impact Analysis, nor is it a comprehensive cost analysis. The following discussion is intended to describe the scope and range of costs that might occur. Many analytical assumptions were necessary to conduct this cost assessment, which is presented in the form of four examples. Each example was conducted independently with no common data sources. The examples are not intended to represent an estimate of the total costs of the rule.

The Agency maintains that a comprehensive analysis of costs would not provide enough additional information to assist Agency management with decisions concerning the rule. A complete analysis of costs for this rule would likely include differential costs to comply with various levels of regulatory control. Similarly, an RIA would likely evaluate alternative options for structuring the rule, where the options might reflect various level of stringency. Due to the complexities of analyzing the impacts of this rule, however, a meaningful cost estimate would be extremely difficult and costly, and it is uncertain whether an RIA would lend reliable information to the decision-making process.

4. Scope of Cost Impacts

Since this rule directly affects only those States that have not adopted their own numeric criteria for toxic pollutants, the cost impacts are limited to dischargers in those States. The cost impacts are further limited by several other factors. First, the potential impact of the rule is limited to treating discharges of only those pollutants included in the rulemaking for each State. In other words, if today's rule imposes criteria for only one pollutant (assuming criteria were adopted and approved for all other pollutants—a situation which occurs for several States), the number of dischargers in that State that might incur compliance costs are limited to dischargers for which that single pollutant drives the treatment needed to comply with their NPDES permit. This situation significantly reduces the number of dischargers with a cost impact. The number of pollutants that could be the basis for additional treatment may be reduced from the number actually included in the rule due to the overlap of controls for groups of pollutants. For example, discharges of several of the metals can be reduced by a single treatment system (generally lime precipitation and clarification) without additional treatment for each additional pollutant in that group.

In some cases, the controls in place—whether installed to comply with technology-based limitations or to comply with a discharge permit issued pursuant to section 304(l) of the Clean Water Act—may be sufficient to provide compliance with water quality criteria. In other cases, controls implemented to meet whole effluent toxicity permit requirements may preclude the need to implement additional controls to reduce a toxic pollutant discharge covered by the rule.

Finally, flow levels, receiving stream conditions, and wasteload allocations are likely to cause variation in the need to install additional treatment technology. For all of these reasons, the Agency believes that the number of dischargers with potential incremental costs is significantly lower than the total number of dischargers in the controlled States.

An estimate of the number of point sources that could be affected begins with the major dischargers from the 14 States included in today's rule.[8] The focus on major dischargers (where the term "major" refers to the distinction used in the NPDES program for facilities with the potential for a significant impact on water quality) is consistent with the rulemaking's focus on toxic pollutants. Any point source with a significant discharge of toxic pollutants is likely to be included in this category.

The number of major facilities for the 18 States is 2,055. (See Footnote 5.) This is a subset of the approximately 7,000 major dischargers in the entire country (3,000 industrial, 4,000 municipal). Of these, 229 facilities already have Individual Control Strategies (ICS) that were established in response to section 304(l) of the Clean Water Act. These facilities have effluent limitations for toxic pollutants sufficient to achieve water quality standards in the receiving water. Thus, the number of major facilities that potentially could be subject to incremental requirements is 1,826. The exact number is likely to be lower because of the number of regulated pollutants in each State and the current discharges of the facilities.

All of the analytical difficulties described above, such as estimating pollutant loadings and compliance costs, would need resolution to accurately estimate the cost impacts for this group of dischargers. In place of attempting to estimate total costs, the following four examples illustrate the range of costs likely to be incurred in specific situations, and some of the problems involved in developing potential compliance costs for this rule.

5. Example: Regulating Dioxin for the Pulp and Paper Industry

As an example of the range of costs that could be associated with the imposition of EPA's numeric criteria, we considered the pulp and paper industry and the pollutant dioxin.

Dioxin (i.e., 2,3,7,8–TCDD, listed as Compound #16 at § 131.35(b) of the proposed rule) is a likely by-product from chlorine bleaching of chemically-pulped wood. Chlorine bleaching is used by approximately 100 pulp mills in the United States. Of those bleach mills, 22 are located in States that had not adopted human health criteria for dioxin as of the date of the proposed

[8] When this assessment was prepared, the Agency contemplated that 18 States would be included in the rule. Thus, the estimated costs described in this preamble are based on a "universe" of 18 States. Since then, four States have adopted and EPA has approved priority toxic pollutant criteria. In the examples that follow, the assessment has not been revised from 18 States to 14 States because the objective of the assessment—to describe the scope and range of impacts—is met even with the higher number of States.

rule. (See Footnote 5.) Thus, this rule could potentially serve as the basis for establishing dioxin limitations in the NPDES permits for those facilities. Of the 22 bleach mills in "unapproved" States, however, 13 already have dioxin limitations in their discharge permits, established in response to section 304(l) of the Clean Water Act. Only for the remaining nine facilities, then, will this rule be a potential reason for establishing dioxin limitations in the discharge permits.

For those nine facilities, however, the effluent levels of dioxin, as reported by the facilities, are all equal to or less than 10 parts per quadrillion (ppq).[6] This effluent data has important implications for projecting costs and impacts. Today's rule will result in water quality standards that contain EPA's human health criteria of 0.013 ppq for dioxin at a 10^{-6} incremental risk level (or 0.13 ppq for States that have expressed a preference for a 10^{-5} incremental risk level). This value would then be reflected in the permits for the facilities that discharge dioxin, after conducting a wasteload allocation and accounting for stream dilution. If the resulting permit limitation is less than 10 ppq, compliance with the permit is likely to be determined at 10 ppq, because that is level of detection for dioxin for the EPA analytical method.

The practical interpretation of the effluent data for these nine facilities is that promulgation of this rule is unlikely to affect the need for treatment and thus, the costs of compliance for water quality-based permits.

These conclusions are very much a function of the laboratory analytical methods and their levels of detection for dioxin. If more precise and reliable measurement becomes available and is incorporated into the monitoring requirements in the permits for these facilities, the small differences between their effluent levels and the more stringent water quality-based limitations could present the need for additional treatment or revised production processes.

The Agency has collected extensive information about the pulp industry's efforts to reduce dioxin discharges from chlorine-bleaching facilities. The industry has responded to the need to reduce dioxin (and related chemicals) discharges with a variety of technological advancements. These include process refinements, such as changing input chemicals or altering the bleaching process. These types of changes are not necessarily prohibitive in terms of investment cost or operating costs. Substantial dioxin reductions have been achieved at little or no incremental compliance costs by changing certain process chemicals. For example, a change to dioxin precursor-free brownstock defoamers has been successful in reducing dioxin discharges at virtually no change in chemical cost and with no additional equipment. Other process chemical changes, however, can result in increased costs. For example, increased chlorine dioxide substitution, which is often accompanied by increased chlorine dioxide generation on-site, has been adopted by various facilities at on investment cost of approximately $20 million each. At the costly extreme, dioxin discharge reductions at other facilities reflect major renovations, not only to reduce dioxin discharges, but to modernize or otherwise restructure the facility. For example, a facility might choose to rebuild its bleach plant and adopt an entirely new bleaching process. Costs for this type of rebuilding may reach $100 million.

In summary, the costs associated with meeting an EPA-imposed dioxin limit can be estimated only with information on the bleaching process currently used at each facility, its wastewater characteristics, the characteristics of the receiving stream, and the level of control mandated by a new water quality-based permit. Based on reported effluent levels, however, this rule is unlikely to be the basis for any incremental compliance costs for Pulp and Paper mills to reduce dioxin discharges.

6. Example: Regulating Copper in the Metal Finishing Industry

As a second example of the range of costs that might be incurred as a result of complying with water quality-based permits issued in response to the imposition of EPA's criteria for toxic pollutants, we considered the metal finishing category for the control of the pollutant copper.

Effluent guidelines limitations and standards, which are technology-based regulations developed by the Agency pursuant to section 304 of the Clean Water Act, were promulgated for this industry in July 1983. Briefly, the effluent guidelines for the metal finishing industry set national standards for all dischargers to surface waters and to wastewater treatment plants (sometimes called publicly-owned treatment works, or POTW). The effluent guidelines for the metal finishing industry include numeric limitations for copper, based on the Best Available Technology Economically Achievable (BAT), for direct dischargers. The limitations for copper, as promulgated, are a daily maximum of 3.38 mg/l and a monthly average of 2.07 mg/l. The technology basis for these limitations is generally lime precipitation and clarification.

When the Agency promulgated effluent guidelines for this industry, the estimated number of direct dischargers subject to the regulation was approximately 2,900. In the Agency's permit compliance database, which reflects a more recent assessment, there are approximately 4,000 metal finishing direct dischargers. The higher, and more conservative number (in terms of projecting the number of affected facilities) is used in this assessment.

Of the 18 States included in this assessment, only six will receive EPA's aquatic criteria for copper; the remainder have already adopted aquatic criteria for copper in their standards.[7] (See Footnote 5.) Approximately 530 of the direct dischargers are located in these six States (where two States account for 93 percent of the facilities).

The number of potentially affected facilities is further reduced for several reasons. First, the number of facilities that would actually be considered for water quality-based permits could be lower, after subtracting any facilities that have individual control strategies (ICSs) to control the discharge of copper. In addition, the Agency has provided a formula in today's rule to allow the permitting authority to determine a water-effect ratio to account for metals speciation. The practical result is that, where determined, the water quality criteria for copper in certain waterbodies is likely to increase. This adjustment will have the effect of bringing the water quality-based limitation closer to the BAT limitation; for some facilities, this water-effect adjustment could eliminate the need for incremental treatment.

Finally, depending on site-specific conditions at each facility, such as the actual discharge concentration of copper, treatment-in-place, and the dilution provided by the receiving stream, complying with the in-stream concentration specified in the rule could be achieved by merely complying with BAT limitations. Alternatively,

[6] U.S. Environmental Protection Agency, Engineering and Analysis Division, "1990 National Census of Pulp, Paper, and Paperboard Manufacturing Facilities—Preliminary Summary Report of Questionnaire Responses for Mills Which Bleach Chemical Pulps," October 31, 1991.

[7] For metal pollutants, such as copper, the aquatic criteria tend to be more stringent than the criteria based on protecting human health. For purposes of this assessment, EPA is estimating impacts related to the aquatic life protection criteria because those criteria are more relevant for establishing water quality standards.

since the in-stream water quality criteria is more stringent than the discharge limitation established by BAT, it is possible that a facility complying with BAT would need additional treatment to comply with a water quality-based limitation.

For purposes of this assessment, EPA investigated whether BAT would be sufficient to meet water quality criteria. Many simplifying assumptions are incorporated into the following discussion. The investigation focused on metal finishing facilities with water releases of the metal pollutants (including, but not limited to copper) as reported in the Toxic Release Inventory.[8] The facilities included in this assessment were limited to those for which plant and stream flow data were readily accessible. While the number of facilities meeting all of these criteria was small, the results were indicative of both scenarios described above. In Connecticut (which is used for illustrative purposes only because it is not included in the final rule), EPA has identified a facility for which BAT will be sufficient for controlling discharges of copper to the level needed to comply with a water quality-based limitation for copper, assuming EPA's criteria level. At that site, the stream dilution is such that meeting the BAT limitation at the discharge point will also likely meet the water quality criteria within the stream. We have also identified another facility in Connecticut for which BAT will not be sufficient—that is, the effluent levels needed to comply with the water quality criteria in the stream are lower than the level that BAT will provide. Thus, additional treatment controls, and incremental compliance costs, are potentially needed for the second facility.

Without a detailed water quality and stream dilution analysis for all dischargers, the number of facilities where BAT will be sufficient to also meet water quality criteria is unknown. For purposes of this assessment, the distribution of facilities where additional treatment may be necessary is assumed to be between 25 and 75 percent. Additionally, the distribution of facility and stream characteristics for metal finishers in Connecticut is assumed to be representative of the distribution of characteristics in the other States. Using these simplifying assumptions, EPA estimates that 130 to 400 facilities are potentially subject to additional treatment requirements.

During the development of the effluent guidelines for this industry, EPA considered several treatment technologies that control pollutant discharges. In addition to the precipitation and clarification technology that was used as the basis for effluent limitations, EPA investigated and published information about effluent filtration, which provides more stringent control of copper discharges.[9] Filtration was not selected as the basis for BAT because of its high cost when considered on a nationwide basis.[10] The removal efficiency for filtration is substantially higher than that for precipitation and clarification. Based on engineering judgment, if filtration were installed at a facility in addition to the technology used as the basis for BAT, meeting the in-stream water quality criteria for copper would be technologically feasible. Hence, the incremental costs for filtration are used here to estimate the range of costs that might be attributable to this rule.

During development of BAT, the Agency estimated total annual costs to add filtration to precipitation and clarification for various sizes of facilities. The incremental cost estimates used here reflect one of several combinations of manufacturing processes and conditions. The costs are likely to be an overestimate because they reflect the upper bound of each flow size range. The potential incremental total annual costs used to estimate the compliance burden for meeting a water quality-based permit are approximately $20,000 for small plants, $43,000 for medium plants, and $146,000 for large plants. To estimate the costs that might be incurred by the dischargers potentially affected by the rule, we assume that the distribution of facility sizes for those dischargers is the same as the distribution used for BAT development. While specific cost estimates depend on many site-specific factors, the range of costs that could be expected for 130 to 400 facilities are approximately $7 million to $20 million.

It is likely that the assessment presented here for copper will include meeting aquatic criteria for other metals due to the similarity in treatment technology. Thus, the cost impacts estimated here will likely provide sufficient treatment to comply with the aquatic criteria for most of the metals.

Another means of considering the potential costs is to evaluate the cost-effectiveness of the additional treatment, where cost-effectiveness is defined by the ratio of incremental cost to incremental pollutant removal. The cost-effectiveness of filtration for those facilities projected to need additional treatment is based on the cost estimates shown above and the pollutant removals for not only copper, but five additional metals that will be removed by filtration. Cost-effectiveness ratios are expressed as "dollars per pound-equivalent removed," where a pound-equivalent is a pound of pollutant weighted by the relative toxicity of that pollutant. The cost-effectiveness of filtration for these facilities is $22 per pound-equivalent removed. This result suggests that filtration is a cost-effective technology.

In summary, the actual burden to dischargers in the metal finishing industry ranges from no impact, where BAT is sufficient to protect the receiving stream, to an incremental cost impact of 5 to 13 percent above the cost of BAT, where filtration is needed. In addition, treatment to comply with more stringent standards appears to be cost-effective.

7. Example: Regulating Priority Pollutants in the Organic Chemicals, Synthetic Fibers, and Plastics Industry

A third example of the range of costs that might be incurred as a result of complying with EPA's criteria for toxic pollutants is based on several segments of the organic chemicals manufacturing industry, where EPA considered the control of all priority pollutant discharges.

Technology-base effluent limitations guidelines and standards were promulgated for this industry in November 1987. The Agency is still engaged in rulemaking activities for this industry in response to litigation and court remands. The following discussion is based on the regulation and supporting documentation from the 1987 final rulemaking.[11]

[8] U.S. Environmental Protection Agency, Toxic Release Inventory, 1989. A search of the inventory for direct dischargers in the metal finishing industry in the six States yielded 41 facilities. Two of the six States have zero facilities matching that description. The comparisons of BAT and water quality criteria are drawn from that subset of the inventory.

[9] U.S. Environmental Protection Agency, Effluent Guidelines Division, Development Document for Effluent Limitations Guidelines and Standards for the Metal Finishing Point Source Category, June 1983.

[10] When establishing BAT, the Clean Water Act requires specific consideration of cost and economic achievability; such consideration is not required when establishing water quality standards. This is not to say that economic considerations are completely outside of the water quality standards process, but that such factors are considered at other points in the process, such as establishing waterbody use classifications. Here, the focus is adopting water quality criteria that are protective of human health and the environment.

[11] U.S. Environmental Protection Agency, Industrial Technology Division, Development Document for Effluent Guidelines and Standards for the Organic Chemicals, Plastics and Synthetic Fibers Point Source Category, Volume I, EPA 440/1-87-009, October 1987.

During development of the effluent guidelines for the organic chemicals industry, the Agency considered the potential for pollutant discharges from all of the priority pollutants. Approximately half of the priority pollutants were detected in effluents from chemical manufacturing facilities, and the effluent guidelines for this industry include limitations for most of these pollutants. The technology basis for establishing BAT varies by pollutant and by industry subcategory, but for many subcategory/pollutant combinations is steam stripping and/or biological treatment.

The promulgated effluent guidelines for the organic chemicals industry were expected to control discharges from more than 700 facilities. Of these, 275 are located in the 18 States used in this assessment to analyze the economic impacts of EPA's human health criteria. (See Footnote 5.) The human health criteria are likely to be the more significant values (compared to aquatic life criteria) for purposes of controlling organic pollutant discharges. The number of direct dischargers in the 18 States is estimated to be 90, based on the total industry proportion of direct dischargers. These dischargers are potentially subject to incremental requirements as a result of today's rule.

The key question for estimating the effect of the rule is whether BAT is sufficient to protect water quality to the levels that would be mandated by imposition of the criteria promulgated today. Water quality modelling results suggest very few exceedances of the water quality criteria, after the imposition of BAT requirements.

The level of control provided by the effluent guideline reflects the analytical laboratory level of detection for nearly half of the regulated pollutants. While the maximum monthly average expressed in the effluent guidelines may be higher than the detection limit (to account for variability), the level of detection corresponds to the long-term average of the treatment's removal efficiency. No water quality exceedances were projected among the pollutants that are regulated at levels higher than the detection limit.

The practical effect of the BAT limitations, combined with levels of detection and water quality assessments, is that this rule is unlikely to affect the behavior of chemical manufacturers in terms of pollution control investments. By complying with BAT limitations, the facilities are likely to also comply with more stringent, water quality-based limitations. Even though EPA's human health criteria suggest that permit requirements for some dischargers will be lower than the level of detection, a facility that cannot demonstrate compliance with the lower permit value is unlikely to add treatment or change processes in response to the revised permit.

In summary, BAT requirements for this industry control nearly half of the regulated pollutants to the level of detection for each pollutant. It is unlikely that the rule will result in incremental economic impacts for direct dischargers in the organic chemicals, plastics, and synthetic fibers industry.

8. Example: Regulating Priority Pollutant for POTWs

The final example of the range of costs that might be incurred as a result of EPA-imposed numeric criteria is for POTWs. An important aspect of regulatory impact for sewage treatment plants is that increases in investment and operating costs are often passed on to consumers in the form of user fees or taxes. For purposes of this assessment, however, we have not extended the cost impacts to household burden.

For POTWs, the choice of treatment technology is dependent on many factors; one of the most important is the pollutant (or group of pollutants) of concern and the source of that pollutant. For example, different technologies are recommended if the pollutants of concern are dissolved organic compounds as opposed to suspended solids. For this assessment, we relied on summary cost information presented in comments the Agency received during development of the Great Lakes Water Quality Initiative and on summary information from a rulemaking that focused on the incremental cost for POTWs to upgrade wastewater treatment.[12] The pollutants of concern and levels of control in those sources are similar to the additional controls that might be imposed by compliance with water quality standards following adoption of EPA's numeric criteria for priority toxic pollutants.

Several comments to the proposed rule contended that reverse osmosis is needed to comply with EPA's criteria for metals. According to commenters, this technology is likely to be very expensive when applied to the high flows found at many POTWs. EPA believes that POTWs often have alternatives to installing this type of treatment technology. These alternatives may be attractive from an overall water quality perspective because they prevent pollution at the source. For example, it may be less expensive for a small number of indirect dischargers to reduce their metals contribution to the POTW's wastestream than for the POTW to treat all of its effluent.

Copper discharges are another potential source of difficulty for POTWs in meeting water quality criteria. Many drinking water systems use copper to control algae growth. The copper is then discharged to the POTW and then to the receiving stream. Other algae controls, such as potassium permanganate, may be effective for some drinking water systems. This example of an alternative would reduce the copper loading to the POTW's receiving stream without requiring expensive treatment such as reverse osmosis at the POTW. Reverse osmosis was not used in either of the cost sources noted above; nor is it used here. The pollution control technology selected for a POTW depends on various engineering judgments and site-specific conditions. The incremental costs used in this assessment are based on activated carbon for some POTWs and on polymer addition for others. Engineering judgment suggests that many of the organic and metal compounds of concern will be removed in the final effluent with these types of treatment technologies.

The following cost assessment is likely to be an overestimate due to the simplifying assumptions used in this procedure. The number of POTWs that possibly could be subject to incremental costs that are attributable to this rule is first limited to POTWs in those States that had not adopted their own numeric criteria by the time of the proposed rulemaking. A total of 18 States was used to project the number of POTWs (See Footnote 5.) Of the approximately 15,000 POTWs in the U.S., 3,942 are identified as "majors" in the Permit Compliance System. Of these, 952 are located in the 18 States. Even as of the proposed rule, however, this number of POTWs is an overestimate of the number that might incur increased costs because it includes *all* States projected to receive *any* pollutant criteria. In fact, many of the 18 states need only a limited number of pollutant criteria (for some States, as few as one).

The number of POTWs that might be subject to new or more stringent permit requirements is further reduced because some portion of those permits already include limitations for some of the pollutants of concern. Such permit limitations and the ICSs were established in response to section 304(l) of the Clean Water Act. Another factor that may eliminate the need for additional treatment by the POTW is the use of whole effluent toxicity limits.

[12] Best Conventional Pollutant Control Technology; Effluent Limitations Guidelines; Final Rule, 51 FR 24974, July 9, 1986.

which are possibly already controlling toxic discharges. In addition, existing treatment and pretreatment may obviate the need for more stringent permit requirements. Other site-specific analyses, such as wasteload allocations and dilution studies are likely to affect the reasonable expectation that a pollutant is discharged. Also, as mentioned earlier, the water-effect ratio calculation is likely to eliminate the need for incremental treatment in certain waterbodies.

For purposes of this assessment, the number of POTWs that will need additional treatment has been estimated by focusing on the results of section 304(l) reviews. During each State's review of dischargers to identify sources that were discharging toxic pollutants at a level that could potentially cause water quality impairments, less than 5 percent of the major municipal dischargers were listed. Applying this proportion to the number of municipal dischargers covered by today's rule yields an estimated 46 POTWs that could potentially cause water quality criteria violations. The provisions of section 304(l) required States to respond to these projected violations by developing Individual Compliance Strategies and permit limitations for toxic pollutants.

The Agency acknowledges that the discharger reviews conducted in response to section 304(l) were not comprehensive and probably undercounted the number of dischargers, including POTWs, that were discharging toxic pollutants. Some of the reasons for undercounting include the lack of monitoring information, quickly-conducted reviews, varying methodologies among States, and out-of-date discharge information. For purposes of this assessment, the number of sources that potentially cause water quality criteria problems is assumed to be three times the number actually listed; in other words, the number of POTWs subject to additional controls is conservatively estimated to be triple the 46 actually identified, or 138 POTWs.

As mentioned, there are various alternatives that an individual POTW might undertake to comply with more stringent permit requirements. While the most costly alternatives involve additional pollution control equipment to the POTW, there are other mechanisms to improve the quality of the POTW's effluent. For example, a pretreatment program could require an industrial discharger to reduce or eliminate its contribution of toxic pollutants to the POTW's wastestream. Alternatively, nonpoint sources could undertake better management practices to reduce runoff. Many of these alternatives have little or no incremental cost impact to the POTW. While some of the alternatives involve a shift in costs, the overall effect is likely to be a lower cost than if incurred solely by the POTW. Even with the availability of alternatives for compliance, this assessment assumes that half of the POTWs will install additional treatment. Hence, 50 percent, or 69, of the potentially affected POTWs are assumed to incur additional compliance costs.

The costs of additional pollution controls are derived from the two sources mentioned above. The cost calculations for activated carbon include capital costs, O&M costs, source controls, and studies (such as mixing zone demonstrations, toxicity testing, monitoring, and fish bio-uptake tests). For purposes of this assessment, simplifying assumptions were then applied to those cost calculations to estimate total annual costs for various sizes of POTWs. The incremental total annual costs for activated carbon are estimated to be $0.4 million for a small POTW, $1.4 million for a medium POTW, and $12.8 million for a large POTW. The cost estimates for improved secondary treatment by polymer addition include annualized capital costs and O&M expenses. The incremental total annual costs for this technology are estimated to be less than $0.1 million for a small POTW, $0.4 million for a medium POTW, and $1.5 million for a large POTW.

Based on engineering judgment, 75 percent of the POTWs are assumed to rely on chemical addition to meet permit limits. The remaining 25 percent are assumed to rely on activated carbon adsorption. To estimate costs for each group of POTWs, the facilities are categorized according to flow groups, assuming that the size distribution of the POTWs in the affected States is the same as those used in each cost source. Then, the incremental costs for each type of treatment are applied to the number of POTWs in each size category. This procedure results in an incremental cost estimate of approximately $30 million.

To summarize, some POTWs may be subject to additional treatment requirements as a result of this rule. The number of POTWs and the types of treatment are dependent on many site-specific conditions and on the pollutants included in today's rule. For many of the POTWs that are major discharges in the States that will need to adopt new water quality standards, there is likely to be no incremental cost. Using a conservative estimate of the remaining POTWs, the upper bound of an incremental cost estimate is approximately $30 million for POTWs to comply with new discharge permit requirements.

9. Conclusions of EPA's Cost Assessment

Today's rule establishes a legal minimum standard where States have failed to comply with the statutory mandate to adopt numeric criteria for toxic pollutants. The impacts to dischargers are difficult to estimate because of the numerous assumptions and unknowns. While the Agency acknowledges that some dischargers may incur compliance costs due to new water quality standards, a meaningful cost estimate that covers the entire rule is not feasible.

In the absence of a cost estimate, per se, the Agency has described the types of costs that may be incurred by various types of dischargers. In addition, this cost assessment includes four examples of potential compliance cost scenarios: reducing dioxin discharges from pulp mills, reducing copper discharges for metal finishing, controlling priority pollutant discharges for organic chemical manufacturing, and reducing discharges from POTWs.

EPA finds that the costs to comply with toxic pollutant criteria may be less than anticipated at the time the rule was proposed. Many States have adopted their own numeric criteria and are therefore excluded from today's rulemaking. In addition, for some point source categories, where technology-based controls have been established, more stringent water quality-based controls will result in no incremental compliance costs. Further, EPA concludes that additional analysis is not warranted because the uncertainty of such an analyses would not provide enough reliable information to assist decision-makers in evaluating the regulatory strategy for this statutorily-mandated rule.

10. Introduction to Benefits Assessment

The numeric criteria for toxic pollutants promulgated in today's rule are essential in implementing toxics controls and protecting human health and aquatic ecosystems. Under this Rule, a total of 15 States and Territories will receive criteria for human health and aquatic life (14 for human health and 13 for aquatic life). The adopted standards will result in decreased toxic pollutant loading discharges which will result in improved protection of human health and aquatic life.

The Agency did not include a quantitative estimate of the benefits in the proposed rule for reasons similar to those cited above for not including a detailed cost estimate. The environmental benefits associated with this promulgation are difficult to assess and quantify. A comprehensive analysis of human health and ecological benefits is not practical given the available resources and inherent limitations such as (1) assuming a linear relationship between pollutant loading reductions and benefits attributed to the clean-up of surface waters; (2) underestimating the benefits or reducing toxics due to the complexity of assessing impacts on aquatic ecosystems; and (3) the uncertainty in estimating the magnitude of intermedia transfers of pollutants. Such uncertainties limit the value of using such estimates to evaluate the net benefits of this rule. However, the Agency has undertaken a preliminary assessment of potential human health and ecological benefits that might be accrued through promulgation of the rule.

11. Human Health Assessment Scope

The potential benefits to human health of establishing toxic criteria include: (1) Reducing the potential health risks to persons eating fish contaminated with toxic pollutants, (2) reducing the potential health risks to persons drinking contaminated drinking water, and (3) reducing the potential health risks to swimmers from dermal exposure to contaminated surface waters. EPA's qualitative assessment is limited to assessing (1) potential benefits from reducing pollutant levels in fish that may be caught by sport and subsistence fishermen and subsequently consumed by them and their families; and (2) potential benefits that may also result from lowering pollutant levels in commercially caught fish consumed by the general population. This assessment is limited to assessing only the potential reduction in cancer risk; no attempt has been made to assess potential reductions in risks due to reproductive, developmental, or other chronic and subchronic toxic effects.

12. Ecological Assessment Scope

Some of the ecological benefits are difficult to assess due to the complexity of ecological interactions, the limited amount of ecological risk information available, and the lack of an established methodology for evaluating ecological benefits. In addition, difficulties arise in estimating the exposure of aquatic ecosystems due to the large size of ecosystems, wide geographical distribution, heterogeneous characteristics and the wide range of populations with differing sensitivities to impacts. While the benefits of promulgating this rule were not quantified due to such uncertainties and limitations, the potential benefits of establishing toxic criteria for the protection of aquatic life can be described qualitatively.

The most recent National Water Quality Inventory indicates that one-third of monitored river miles, lake acres, and coastal waters have elevated levels of toxic pollutants. After evaluating these data, the Agency concluded that the data most likely understate the presence or discharge of toxic pollutants because of the limited amount of monitoring data for some States and inconsistencies among the States in how the data were generated. Thus, it is likely that significant portions of water bodies in some States exceed water quality criteria for the protection of aquatic life. These criteria were developed to protect most aquatic organisms, as well as wildlife that consume aquatic organisms, from acute and chronic toxic effects that adversely affect survival, growth or reproduction. These effects will vary due to the diversity of species with differing sensitivities to impacts. For example, lead exposure can cause spinal deformities in rainbow trout. Nickel exposure can affect spawning behavior of shrimp. Nickel, mercury, and copper exposure can affect the growth activity of algae. In addition, copper, mercury, and cadmium can be acutely toxic to aquatic life including finfish. These types of ecological effects are expected to be reduced because this rule should reduce ambient pollutant levels. In addition, this rule will reduce continuous discharges of toxics which will allow for a natural recovery of the ecosystems.

13. Qualitative Benefits Assessment

Human health benefits that can be attributed to this rule are expressed in terms of the reduction in cancer risk. The analysis performed was limited to assessing only the potential reduction in cancer risk; no assessment of potential reductions in risks due to reproductive, developmental, or other chronic and subchronic toxic effects was conducted. However, given the number of pollutants, there could be: (1) Decreased incidence of systemic toxicity to vital organs such as liver and kidney; (2) decreased extent of learning disability and intellectual impairment due to the exposure to such pollutants as lead; and (3) decreased risk of adverse reproductive effects and genotoxicity.

The ecological benefits that can be expected from today's rule include protection of both fresh and salt water organisms, as well as wildlife that consume aquatic organisms. Today's rule will result in a reduction in the presence and discharge of toxic pollutants in the water bodies of these States thereby protecting those aquatic ecosystems currently under stress, providing the opportunity for the reestablishment of productive ecosystems in damaged water bodies, and protection of resident endangered species.

In addition, the rule would result in the propagation and productivity of fish and other organisms, maintaining fisheries for both commercial and recreational purposes. Recreational activities such as boating, water skiing, and swimming would also be preserved along with the maintenance of an aesthetically pleasing environment. Both recreational and commercial activities contribute, in turn, to the support of local and State economies.

K. Regulatory Flexibility Act

The Regulatory Flexibility Act (5 U.S.C. 601 et seq., Pub. L. 96-354) requires EPA to assess whether its regulations create a disproportionate effect on small entities. Among its provisions, the Act directs EPA to prepare and publish an initial regulatory flexibility analysis at the time a rule is proposed if the rule will have a significant impact on a substantial number of small entities. In the preamble to the proposed rule, EPA discussed the possibility that the rule could result in treatment costs to some dischargers to comply with water quality standards that incorporate new criteria for toxic pollutants. The Agency did not conclude, however, that the rule would have a significant impact on a substantial number of small entities due to the uncertainties associated with estimating total costs and impacts. The difficulties of cost estimation for specific groups of dischargers (such as small businesses or governments) were described in the preamble section that outlined EPA's response to Executive Order 12291. Similarly, in today's final rulemaking, the details of EPA's findings concerning the costs and impacts of this rule are presented in section J, above.

Briefly, the complexities and difficulties associated with estimating costs for purposes of economic or regulatory analysis similarly apply to estimating impacts to small entities. For purposes of this rulemaking, small entities are small dischargers, whether industrial or municipal. Regardless of

the parameters used to define small dischargers (for example, discharge flow, number of employees, population served), EPA's expression of costs and impacts for this rulemaking is limited to the descriptions in section J. EPA does not find that there will be a significant impact on a substantial number of small entities because impacts on specific dischargers cannot be predicted with certainty, and based on several examples in the cost assessment, it appears that potential impacts will not be concentrated among small dischargers.

In addition, EPA again finds that the impacts on small entities are best considered during standards development and implementation when site-specific costs can be estimated, and any resulting impacts can be minimized or alleviated as part of writing the discharge permit. It is not the Agency's intent to ignore the consequences of incorporating toxic pollutant criteria, but instead, that these consequences are more appropriately defined and accounted for in the permit-writing context. The water quality standards regulation provides several means (such as adjusting designated uses, setting site-specific criteria, or granting variances) to consider costs and adjust standards to account for the impacts on small dischargers.

While the imposition of EPA's numeric criteria for toxic pollutants may limit the flexibility that States will have to use these procedures to modify standards, EPA's expectation is that impacts will not be concentrated on small dischargers. Although there can be site-specific cases of water quality violations due to toxic discharges from low-flow point sources, EPA generally finds that priorities for NPDES permits focus on major dischargers. Small entities are less likely to be included in this group.

Other requirements of the Regulatory Flexibility Act are fulfilled in other sections of this preamble. Specifically, the Agency's explanation for taking this action and the legal basis for the rule are found in section E. The number of small entities that will be affected by the rule is not estimated for the reasons expressed above. The projected reporting and recordkeeping requirements are discussed in Section L. There is no anticipated duplication, overlap, or conflict with other Federal rules, except to the extent that technology-based standards (such as BAT) are sufficient to also meet water quality standards. Alternatives to the final rule include any of the opportunities that States had to adopt their own standards, incorporating any of the procedures to limit the compliance burden; these alternatives are discussed in Sections B and C.

The Agency concludes that this rulemaking, *per se*, will not result in a significant impact on a substantial number of small entities, and a final regulatory flexibility analysis is not required.

L. Paperwork Reduction Act

The information collection requirements in this rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. These requirements will not be effective until OMB approves them and a technical amendment to that effect is published in the Federal Register. An Information Collection Request (ICR) document has been prepared by EPA (ICR No. 0988.04) and a copy may be obtained from Sandy Farmer, Information Policy Branch; EPA; 401 M St., SW. (PM–223Y); Washington, DC 20460 or by calling (202) 260–2740.

Public reporting burden for this collection of information is estimated to average 725 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM–223Y, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs; Office of Management and Budget, Washington, DC 20503, marked "Attention: Desk Officer for EPA." Comments must be submitted by January 21, 1993.

List of Subjects in 40 CFR Part 131

Water pollution control, Water quality standards, Toxic pollutants.

Dated: December 1, 1992.

William K. Reilly,

Administrator.

For the reasons set out in the preamble title 40, chapter I, part 131 of the Code of Federal Regulations is amended as follows:

PART 131—WATER QUALITY STANDARDS

1. The authority citation for part 131 is revised to read as follows:

Authority: 33 U.S.C. 1251 et seq.

Subpart D—[Amended]

2. Section 131.36 is added to subpart D to read as follows:

§ 131.36 Toxics criteria for those states not complying with Clean Water Act section 303(c)(2)(B).

(a) *Scope.* This section is not a general promulgation of the section 304(a) criteria for priority toxic pollutants but is restricted to specific pollutants in specific States.

(b)(1) *EPA's Section 304(a) Criteria for Priority Toxic Pollutants.*

BILLING CODE 6560-50-M

(#) COMPOUND	CAS Number	B FRESHWATER Criterion Maximum Conc. d (ug/L) B1	B FRESHWATER Criterion Continuous Conc. d (ug/L) B2	C SALTWATER Criterion Maximum Conc. d (ug/L) C1	C SALTWATER Criterion Continuous Conc. d (ug/L) C2	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Water & Organisms (ug/L) D1	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Organisms Only (ug/L) D2
1 Antimony	7440360					14 a	4300 a
2 Arsenic	7440382	360 m	190 m	69 m	36 m	0.018 a,b,c	0.14 a,b,c
3 Beryllium	7440417					n	n
4 Cadmium	7440439	3.9 e,m	1.1 e,m	43 m	9.3 m	n	n
5a Chromium (III)	16065831	1700 e,m	210 e,m			n	n
b Chromium (VI)	18540299	16 m	11 m	1100 m	50 m	n	n
6 Copper	7440508	18 e,m	12 e,m	2.9 m	2.9 m		
7 Lead	7439921	82 e,m	3.2 e,m	220 m	8.5 m	n	n
8 Mercury	7439976	2.4 m	0.012 i	2.1 m	0.025 i	0.14	0.15
9 Nickel	7440020	1400 e,m	160 e,m	75 m	8.3 m	610 a	4600 a
10 Selenium	7782492	20	5	300 m	71 m	n	n
11 Silver	7440224	4.1 e,m		2.3 m			
12 Thallium	7440280					1.7 a	6.3 a
13 Zinc	7440666	120 e,m	110 e,m	95 m	86 m		
14 Cyanide	57125	22	5.2	1	1	700 a	220000 a,j
15 Asbestos	1332214					7,000,000 fibers/L k	
16 2,3,7,8-TCDD (Dioxin)	1746016					0.000000013 c	0.000000014 c
17 Acrolein	107028					320	780
18 Acrylonitrile	107131					0.059 a,c	0.66 a,c
19 Benzene	71432					1.2 a,c	71 a,c
20 Bromoform	75252					4.3 a,c	360 a,c
21 Carbon Tetrachloride	56235					0.25 a,c	4.4 a,c
22 Chlorobenzene	108907					680 a	21000 a,j
23 Chlorodibromomethane	124481					0.41 a,c	34 a,c
24 Chloroethane	75003						
25 2-Chloroethylvinyl Ether	110758						
26 Chloroform	67663					5.7 a,c	470 a,c
27 Dichlorobromomethane	75274					0.27 a,c	22 a,c

(#) COMPOUND	CAS Number	B FRESHWATER Criterion Maximum Conc. d (ug/L) B1	B FRESHWATER Criterion Continuous Conc. d (ug/L) B2	C SALTWATER Criterion Maximum Conc. d (ug/L) C1	C SALTWATER Criterion Continuous Conc. d (ug/L) C2	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Water & Organisms (ug/L) D1	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Organisms Only (ug/L) D2
28 1,1-Dichloroethane	75343						
29 1,2-Dichloroethane	107062					0.38 a,c	99 a,c
30 1,1-Dichloroethylene	75354					0.057 a,c	3.2 a,c
31 1,2-Dichloropropane	78875						
32 1,3-Dichloropropylene	542756					10 a	1700 a
33 Ethylbenzene	100414					3100 a	29000 a
34 Methyl Bromide	74839					48 a	4000 a
35 Methyl Chloride	74873					n	n
36 Methylene Chloride	75092					4.7 a,c	1600 a,c
37 1,1,2,2-Tetrachloroethane	79345					0.17 a,c	11 a,c
38 Tetrachloroethylene	127184					0.8 c	8.85 c
39 Toluene	108883					6800 a	200000 a
40 1,2-Trans-Dichloroethylene	156605						
41 1,1,1-Trichloroethane	71556					n	n
42 1,1,2-Trichloroethane	79005					0.60 a,c	42 a,c
43 Trichloroethylene	79016					2.7 c	81 c
44 Vinyl Chloride	75014					2 c	525 c
45 2-Chlorophenol	95578						
46 2,4-Dichlorophenol	120832					93 a	790 a,j
47 2,4-Dimethylphenol	105679						
48 2-Methyl-4,6-Dinitrophenol	534521					13.4	765
49 2,4-Dinitrophenol	51285					70 a	14000 a
50 2-Nitrophenol	88755						
51 4-Nitrophenol	100027						
52 3-Methyl-4-Chlorophenol	59507						
53 Pentachlorophenol	87865	20 f	13 f	13	7.9	0.28 a,c	8.2 a,c,j
54 Phenol	108952					21000 a	4600000 a,j
55 2,4,6-Trichlorophenol	88062					2.1 a,c	6.5 a,c
56 Acenaphthene	83329						

#)	A COMPOUND	CAS Number	B FRESHWATER Criterion Maximum Conc. d (ug/L) B1	B FRESHWATER Criterion Continuous Conc. d (ug/L) B2	C SALTWATER Criterion Maximum Conc. d (ug/L) C1	C SALTWATER Criterion Continuous Conc. d (ug/L) C2	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Water & Organisms (ug/L) D1	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Organisms Only (ug/L) D2
57	Acenaphthylene	208968						
58	Anthracene	120127					9600 a	110000 a
59	Benzidine	92875					0.00012 a,c	0.00054 a,c
60	Benzo(a)Anthracene	56553					0.0028 c	0.031 c
61	Benzo(a)Pyrene	50328					0.0028 c	0.031 c
62	Benzo(b)Fluoranthene	205992					0.0028 c	0.031 c
63	Benzo(ghi)Perylene	191242						
64	Benzo(k)Fluoranthene	207089					0.0028 c	0.031 c
65	Bis(2-Chloroethoxy)Methane	111911						
66	Bis(2-Chloroethyl)Ether	111444					0.031 a,c	1.4 a,c
67	Bis(2-Chloroisopropyl)Ether	108601					1400 a	170000 a
68	Bis(2-Ethylhexyl)Phthalate	117817					1.8 a,c	5.9 a,c
69	4-Bromophenyl Phenyl Ether	101553						
70	Butylbenzyl Phthalate	85687						
71	2-Chloronaphthalene	91587						
72	4-Chlorophenyl Phenyl Ether	7005723						
73	Chrysene	218019					0.0028 c	0.031 c
74	Dibenzo(a,h)Anthracene	53703					0.0028 c	0.031 c
75	1,2-Dichlorobenzene	95501					2700 a	17000 a
76	1,3-Dichlorobenzene	541731					400	2600
77	1,4-Dichlorobenzene	106467					400	2600
78	3,3'-Dichlorobenzidine	91941					0.04 a,c	0.077 a,c
79	Diethyl Phthalate	84662					23000 a	120000 a
80	Dimethyl Phthalate	131113					313000	2900000
81	Di-n-Butyl Phthalate	84742					2700 a	12000 a
82	2,4-Dinitrotoluene	121142					0.11 c	9.1 c
83	2,6-Dinitrotoluene	606202						
84	Di-n-Octyl Phthalate	117840						
85	1,2-Diphenylhydrazine	122667					0.040 a,c	0.54 a,c

(#)	A COMPOUND	CAS Number	B FRESHWATER Criterion Maximum Conc. d (ug/L) B1	B FRESHWATER Criterion Continuous Conc. d (ug/L) B2	C SALTWATER Criterion Maximum Conc. d (ug/L) C1	C SALTWATER Criterion Continuous Conc. d (ug/L) C2	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Water & Organisms (ug/L) D1	D HUMAN HEALTH (10^{-6} risk for carcinogens) For Consumption of: Organisms Only (ug/L) D2
86	Fluoranthene	206440					300 a	370 a
87	Fluorene	86737					1300 a	14000 a
88	Hexachlorobenzene	118741					0.00075 a,c	0.00077 a,c
89	Hexachlorobutadiene	87683					0.44 a,c	50 a,c
90	Hexachlorocyclopentadiene	77474					240 a	17000 a,j
91	Hexachloroethane	67721					1.9 a,c	8.9 a,c
92	Indeno(1,2,3-cd)Pyrene	193395					0.0028 c	0.031 c
93	Isophorone	78591					8.4 a,c	600 a,c
94	Naphthalene	91203						
95	Nitrobenzene	98953					17 a	1900 a,j
96	N-Nitrosodimethylamine	62759					0.00069 a,c	8.1 a,c
97	N-Nitrosodi-n-Propylamine	621647						
98	N-Nitrosodiphenylamine	86306					5.0 a,c	16 a,c
99	Phenanthrene	85018						
100	Pyrene	129000					960 a	11000 a
101	1,2,4-Trichlorobenzene	120821						
102	Aldrin	309002	3 g		1.3 g		0.00013 a,c	0.00014 a,c
103	alpha-BHC	319846					0.0039 a,c	0.013 a,c
104	beta-BHC	319857					0.014 a,c	0.046 a,c
105	gamma-BHC	58899	2 g	0.08 g	0.16 g		0.019 c	0.063 c
106	delta-BHC	319868						
107	Chlordane	57749	2.4 g	0.0043 g	0.09 g	0.004 g	0.00057 a,c	0.00059 a,c
108	4-4'-DDT	50293	1.1 g	0.001 g	0.13 g	0.001 g	0.00059 a,c	0.00059 a,c
109	4,4'-DDE	72559					0.00059 a,c	0.00059 a,c
110	4,4'-DDD	72548					0.00083 a,c	0.00084 a,c
111	Dieldrin	60571	2.5 g	0.0019 g	0.71 g	0.0019 g	0.00014 a,c	0.00014 a,c
112	alpha-Endosulfan	959988	0.22 g	0.056 g	0.034 g	0.0087 g	0.93 a	2.0 a
113	beta-Endosulfan	33213659	0.22 g	0.056 g	0.034 g	0.0087 g	0.93 a	2.0 a

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114	Endosulfan Sulfate	1031078					0.93 a	2.0 a
115	Endrin	72208	0.18 g	0.0023 g	0.037 g	0.0023 g	0.76 a	0.81 a,i
116	Endrin Aldehyde	7421934					0.76 a	0.81 a,i
117	Heptachlor	76448	0.52 g	0.0038 g	0.053 g	0.0036 g	0.00021 a,c	0.00021 a,c
118	Heptachlor Epoxide	1024573	0.52 g	0.0038 g	0.053 g	0.0036 g	0.00010 a,c	0.00011 a,c
119	PCB-1242	53469219		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
120	PCB-1254	11097691		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
121	PCB-1221	11104282		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
122	PCB-1232	11141165		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
123	PCB-1248	12672296		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
124	PCB-1260	11096825		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
125	PCB-1016	12674112		0.014 g		0.03 g	0.000044 a,c	0.000045 a,c
126	Toxaphene	8001352	0.73	0.0002	0.21	0.0002	0.00073 a,c	0.00075 a,c
Total No. of Criteria (h) =			24	29	23	27	91	98

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Footnotes:

a. Criteria revised to reflect current agency q_1^* or RfD, as contained in the Integrated Risk Information System (IRIS). The fish tissue bioconcentration factor (BCF) from the 1980 criteria documents was retained in all cases.

b. The criteria refers to the inorganic form only.

c. Criteria in the matrix based on carcinogenicity (10^{-6} risk). For a risk level of 10^{-5}, move the decimal point in the matrix value one place to the right.

d. Criteria Maximum Concentration (CMC) = the highest concentration of a pollutant to which aquatic life can be exposed for a short period of time (1-hour average) without deleterious effects. Criteria Continuous Concentration (CCC) = the highest concentration of a pollutant to which aquatic life can be exposed for an extended period of time (4 days) without deleterious effects. ug/L = micrograms per liter

e. Freshwater aquatic life criteria for these metals are expressed as a function of total hardness (mg/L), and as a function of the pollutant's water effect ratio, WER, as defined in § 131.36(c). The equations are provided in matrix at § 131.36(b)(2). Values displayed above in the matrix correspond to a total hardness of 100 mg/L and a water effect ratio of 1.0.

f. Freshwater aquatic life criteria for pentachlorophenol are expressed as a function of pH, and are calculated as follows. Values displayed above in the matrix correspond to a pH of 7.8.

$CMC = \exp\{1.005(pH) - 4.830\}$ $CCC = \exp\{1.005(pH) - 5.290\}$

g. Aquatic life criteria for these compounds were issued in 1980 utilizing the 1980 Guidelines for criteria development. The acute values shown are final acute values (FAV) which by the 1980 Guidelines are instantaneous values as contrasted with a CMC which is a one-hour average.

h. These totals simply sum the criteria in each column. For aquatic life, there are 30 priority toxic pollutants with some type of freshwater or saltwater, acute or chronic criteria. For human health, there are 91 priority toxic pollutants with either "water + fish" or "fish only" criteria. Note that these totals count chromium as one pollutant even though EPA has developed criteria based on two valence states. In the matrix, EPA has assigned numbers 5a and 5b to the criteria for chromium to reflect the fact that the list of 126 priority toxic pollutants includes only a single listing for chromium.

i. If the CCC for total mercury exceeds 0.012 ug/L more than once in a 3-year period in the ambient water, the edible portion of aquatic species of concern must be analyzed to determine whether the concentration of methyl mercury exceeds the FDA action level (1.0 mg/kg). If the FDA action level is exceeded, the State must notify the appropriate EPA Regional Administrator, initiate a revision of its mercury criterion in its water quality standards so as to protect designated uses, and take other appropriate action such as issuance of a fish consumption advisory for the affected area.

j. No criteria for protection of human health from consumption of aquatic organisms (excluding water) was presented in the 1980 criteria document or in the 1986 Quality Criteria for Water. Nevertheless, sufficient information was presented in the 1980 document to allow a calculation of a criterion, even though the results of such a calculation were not shown in the document.

k. The criterion for asbestos is the MCL (56 FR 3526, January 30, 1991).

l. This letter not used as a footnote.

m. Criteria for these metals are expressed as a function of the water effect ratio, WER, as defined in 40 CFR 131.36(c).

CMC = column B1 or C1 value × WER
CCC = column B2 or C2 value × WER

n. EPA is not promulgating human health criteria for this contaminant. However, permit authorities should address this contaminant in NPDES permit actions using the State's existing narrative criteria for toxics.

General Notes:

1. This chart lists all of EPA's priority toxic pollutants whether or not criteria recommendations are available. Blank spaces indicate the absence of criteria recommendations. Because of variations in chemical nomenclature systems, this listing of toxic pollutants does not duplicate the listing in Appendix A of 40 CFR Part 423. EPA has added the Chemical Abstracts Service (CAS) registry numbers, which provide a unique identification for each chemical.

2. The following chemicals have organoleptic based criteria recommendations that are not included on this chart (for reasons which are discussed in the preamble): copper, zinc, chlorobenzene, 2-chlorophenol, 2,4-dichlorophenol, acenaphthene, 2,4-dimethylphenol, 3-methyl-4-chlorophenol, hexachlorocyclopentadiene, pentachlorophenol, phenol

3. For purposes of this rulemaking, freshwater criteria and saltwater criteria apply as specified in 40 CFR 131.36(c).

(2) *Factors for Calculating Metals Criteria*

$CMC = WER \exp\{m_A[\ln(\text{hardness})] + b_A\}$ $CCC = WER \exp\{m_C[\ln(\text{hardness})] + b_C\}$

	m_A	b_A	m_C	b_C
Cadmium	1.128	-3.828	0.7852	-3.490
Copper	0.9422	-1.464	0.8545	-1.465
Chromium (III)	0.8190	3.688	0.8190	1.561
Lead	1.273	-1.460	1.273	-4.705
Nickel	0.8460	3.3612	0.8460	1.1645
Silver	1.72	-6.52	.....	.....
Zinc	0.8473	0.8604	0.8473	0.7614

Note: The term "exp" represents the base e exponential function.

(c) *Applicability.* (1) The criteria in paragraph (b) of this section apply to the States' designated uses cited in paragraph (d) of this section and supersede any criteria adopted by the State, except when State regulations contain criteria which are more stringent for a particular use in which case the State's criteria will continue to apply.

(2) The criteria established in this section are subject to the State's general rules of applicability in the same way and to the same extent as are the other numeric toxics criteria when applied to the same use classifications including mixing zones, and low flow values below which numeric standards can be exceeded in flowing fresh waters.

(i) For all waters with mixing zone regulations or implementation procedures, the criteria apply at the appropriate locations within or at the boundary of the mixing zones; otherwise the criteria apply throughout the waterbody including at the end of any discharge pipe, canal or other discharge point.

(ii) A State shall not use a low flow value below which numeric standards can be exceeded that is less stringent than the following for waters suitable for the establishment of low flow return frequencies (i.e., streams and rivers):

Aquatic Life	
Acute criteria (CMC)	1 Q 10 or 1 B 3
Chronic criteria (CCC)	7 Q 10 or 4 B 3

Human Health	
Non-carcinogens	30 Q 5
Carcinogens	Harmonic mean flow

Where:

CMC—criteria maximum concentration—the water quality criteria to protect against acute effects in aquatic life and is the highest instream concentration of a priority toxic pollutant consisting of a one-hour average

not to be exceeded more than once every three years on the average;

CCC—criteria continuous concentration—the water quality criteria to protect against chronic effects in aquatic life is the highest instream concentration of a priority toxic pollutant consisting of a 4-day average not to be exceeded more than once every three years on the average;

1 Q 10 is the lowest one day flow with an average recurrence frequency of once in 10 years determined hydrologically;

1 B 3 is biologically based and indicates an allowable exceedence of once every 3 years. It is determined by EPA's computerized method (DFLOW model);

7 Q 10 is the lowest average 7 consecutive day low flow with an average recurrence frequency of once in 10 years determined hydrologically;

4 B 3 is biologically based and indicates an allowable exceedence for 4 consecutive days once every 3 years. It is determined by EPA's computerized method (DFLOW model);

30 Q 5 is the lowest average 30 consecutive day low flow with an average recurrence frequency of once in 5 years determined hydrologically; and the harmonic mean flow is a long term mean flow value calculated by dividing the number of daily flows analyzed by the sum of the reciprocals of those daily flows.

(iii) If a State does not have such a low flow value for numeric standards compliance, then none shall apply and the criteria included in paragraph (d) of this section herein apply at all flows.

(3) The aquatic life criteria in the matrix in paragraph (b) of this section apply as follows:

(i) For waters in which the salinity is equal to or less than 1 part per thousand 95% or more of the time, the applicable criteria are the freshwater criteria in Column B;

(ii) For waters in which the salinity is equal to or greater than 10 parts per thousand 95% or more of the time, the applicable criteria are the saltwater criteria in Column C; and

(iii) For waters in which the salinity is between 1 and 10 parts per thousand as defined in paragraphs (c)(3) (i) and (ii) of this section, the applicable criteria are the more stringent of the freshwater or saltwater criteria. However, the Regional Administrator may approve the use of the alternative freshwater or saltwater criteria if scientifically defensible information and data demonstrate that on a site-specific basis the biology of the waterbody is dominated by freshwater aquatic life and that freshwater criteria are more appropriate; or conversely, the biology of the waterbody is dominated by saltwater aquatic life and that saltwater criteria are more appropriate.

(4) *Application of metals criteria.* (i) For purposes of calculating freshwater aquatic life criteria for metals from the equations in paragraph (b)(2) of this section, the minimum hardness allowed for use in those equations shall not be less than 25 mg/l, as calcium carbonate, even if the actual ambient hardness is less than 25 mg/l as calcium carbonate. The maximum hardness value for use in those equations shall not exceed 400 mg/l as calcium carbonate, even if the actual ambient hardness is greater than 400 mg/l as calcium carbonate. The same provisions apply for calculating the metals criteria for the comparisons provided for in paragraph (c)(3)(iii) of this section.

(ii) The hardness values used shall be consistent with the design discharge conditions established in paragraph (c)(2) of this section for flows and mixing zones.

(iii) The criteria for metals (compounds #1–#13 in paragraph (b) of this section) are expressed as total recoverable. For purposes of calculating aquatic life criteria for metals from the equations in footnote M. in the criteria matrix in paragraph (b)(1) of this section and the equations in paragraph (b)(2) of this section, the water-effect ratio is computed as a specific pollutant's acute or chronic toxicity values measured in water from the site covered by the standard, divided by the respective acute or chronic toxicity value in laboratory dilution water. The water-effect ratio shall be assigned a value of 1.0, except where the permitting authority assigns a different value that protects the designated uses of the water body from the toxic effects of the pollutant, and is derived from suitable tests on sampled water representative of conditions in the affected water body, consistent with the design discharge conditions established in paragraph (c)(2) of this section. For purposes of this paragraph, the term acute toxicity value is the toxicity test results, such as the lethal concentration of one-half of the test organisms (i.e., LC50) after 96 hours of exposure (e.g., fish toxicity tests) or the effect concentration to one-half of the test organisms, (i.e., EC50) after 48 hours of exposure (e.g., daphnia toxicity tests). For purposes of this paragraph, the term chronic value is the result from appropriate hypothesis testing or regression analysis of measurements of growth, reproduction, or survival from life cycle, partial life cycle, or early life stage tests. The determination of acute and chronic values shall be according to current standard protocols (e.g., those published by the American Society for Testing Materials (ASTM)) or other comparable methods. For calculation of criteria using site-specific values for both the hardness and the water effect ratio, the hardness used in the equations in paragraph (b)(2) of this section shall be as required in paragraph (c)(4)(ii) of this section. Water hardness shall be calculated from the measured calcium and magnesium ions present, and the ratio of calcium to magnesium shall be approximately the same in standard laboratory toxicity testing water as in the site water.

(d) *Criteria for Specific Jurisdictions*—(1) *Rhode Island, EPA Region 1.* (i) All waters assigned to the following use classifications in the Water Quality Regulations for Water Pollution Control adopted under Chapters 46–12, 42–17.1, and 42–35 of the General Laws of Rhode Island are subject to the criteria in paragraph (d)(1)(ii) of this section, without exception:

6.21 Freshwater	6.22 Saltwater:
Class A	Class SA
Class B	Class SB
Class C	Class SC

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(1)(i) of this section:

Use classification	Applicable criteria
Class A Class B waters where water supply use is designated	These classifications are assigned the criteria in: Column D1—all
Class B waters where water supply use is not designated; Class C; Class SA; Class SB; Class SC	Each of these classifications is assigned the criteria in: Column D2—all

(iii) The human health criteria shall be applied at the 10^{-5} risk level, consistent with the State policy. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(2) *Vermont, EPA Region 1.* (i) All waters assigned to the following use classifications in the Vermont Water Quality Standards adopted under the authority of the Vermont Water Pollution Control Act (10 V.S.A., Chapter 47) are subject to the criteria in paragraph (d)(2)(ii) of this section, without exception:

Class A
Class B
Class C

(ii) The following criteria from the matrix in paragraph (b)(1) of this section

apply to the use classifications identified in paragraph (d)(2)(i) of this section:

Use classification	Applicable criteria
Class A	
Class B waters where water supply use is designated	This classification is assigned the criteria in: Column B1—all Column B2—all Column D1—all
Class B waters where water supply use is not designated	
Class C	These classifications are assigned the criteria in: Column B1—all Column B2—all Column D2—all

(iii) The human health criteria shall be applied at the State-proposed 10^{-6} risk level.

(3) *New Jersey, EPA Region 2.* (i) All waters assigned to the following use classifications in the New Jersey Administrative Code (N.J.A.C.) 7:9–4.1 et seq., Surface Water Quality Standards, are subject to the criteria in paragraph (d)(3)(ii) of this section, without exception.

N.J.A.C. 7:9–4.12(b): Class PL
N.J.A.C. 7:9–4.12(c): Class FW2
N.J.A.C. 7:9–4.12(d): Class SE1
N.J.A.C. 7:9–4.12(e): Class SE2
N.J.A.C. 7:9–4.12(f): Class SE3
N.J.A.C. 7:9–4.12(g): Class SC
N.J.A.C. 7:9–4.13(a): Delaware River Zones 1C, 1D, and 1E
N.J.A.C. 7:9–4.13(b): Delaware River Zone 2
N.J.A.C. 7:9–4.13(c): Delaware River Zone 3
N.J.A.C. 7:9–4.13(d): Delaware River Zone 4
N.J.A.C. 7:9–4.13(e): Delaware River Zone 5
N.J.A.C. 7:9–4.13(f): Delaware River Zone 6

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(3)(i) of this section:

Use classification	Applicable criteria
PL (Freshwater Pinelands), FW2	These classifications are assigned the criteria in: Column B1—all except #102, 105, 107, 108, 111, 112, 113, 115, 117, and 118. Column B2—all except #105, 107, 108, 111, 112, 113, 115, 117, 118, 119, 120, 121, 122, 123, 124, and 125.
PL (Saline Water Pinelands), SE1, SE2, SE3, SC	These classifications are each assigned the criteria in: Column C1—all except #102, 105, 107, 108, 111, 112, 113, 115, 117, and 118. Column C2—all except #105, 107, 108, 111, 112, 113, 115, 117, 118, 119, 120, 121, 122, 123, 124, and 125. Column D2—all at a 10^{-6} risk level except #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105; #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105, at a 10^{-5} risk level.
Delaware River zones 1C, 1D, 1E, 2, 3, 4, 5 and Delaware Bay zone 6	These classifications are each assigned the criteria in: Column B1—all. Column B2—all. Column D1—all at a 10^{-6} risk level except #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105; #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105, at a 10^{-5} risk level. Column D2—all at a 10^{-6} risk level except #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105; #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105, at a 10^{-5} risk level.
Delaware River zones 3, 4, and 5, and Delaware Bay zone 6	These classifications are each assigned the criteria in: Column C1—all. Column C2—all. Column D2—all at a 10^{-6} risk level except #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105; #23, 30, 37, 38, 42, 68, 89, 91, 93, 104, 105, at a 10^{-5} risk level.

(iii) The human health criteria shall be applied at the State-proposed 10^{-6} risk level for EPA rated Class A, B_1, and B_2 carcinogens; EPA rated Class C carcinogens shall be applied at 10^{-5} risk level. To determine appropriate value for carcinogens, see footnote c. in the matrix in paragraph (b)(1) of this section.

(4) *Puerto Rico, EPA Region 2.* (i) All waters assigned to the following use classifications in the Puerto Rico Water Quality Standards (promulgated by Resolution Number R–83–5–2) are subject to the criteria in paragraph (d)(4)(ii) of this section, without exception:

Article 2.2.2—Class SB
Article 2.2.3—Class SC
Article 2.2.4—Class SD

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(4)(i) of this section:

Use classification	Applicable criteria
Class SD	This Classification is assigned criteria in: Column B1—all, except: 10, 102, 105, 107, 108, 111, 112, 113, 115, 117, and 126. Column B2—all, except: 105, 107, 108, 112, 113, 115, and 117. Column D1—all, except: 6, 14, 105, 112, 113, and 115. Column D2—all, except: 14, 105, 112, 113, and 115.
Class SB, Class SC	These Classifications are assigned criteria in:

Use classification	Applicable criteria
	Column C1—all, except: 4, 5b, 7, 8, 10, 11, 13, 102, 105, 107, 108, 111, 112, 113, 115, 117, and 126.
	Column C2—all, except: 4, 5b, 10, 13, 108, 112, 113, 115, and 117.
	Column D2—all, except: 14, 105, 112, 113, and 115.

(iii) The human health criteria shall be applied at the State-proposed 10^{-5} risk level. To determine appropriate value for carcinogens, see footnote c, in the criteria matrix in paragraph (b)(1) of this section.

(5) *District of Columbia, EPA Region 3.*

(i) All waters assigned to the following use classifications in chapter 11 Title 21 DCMR, Water Quality Standards of the District of Columbia are subject to the criteria in paragraph (d)(5)(ii) of this section, without exception:

1101.2 Class C waters

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classification identified in paragraph (d)(5)(i) of this section:

Use classification	Applicable criteria
Class C	This classification is assigned the additional criteria in: Column B2—#10, 118, 126. Column D1—#15, 16, 44, 67, 68, 79, 80, 81, 88, 114, 116, 118. Column D2—all.

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(6) *Florida, EPA Region 4.*

(i) All waters assigned to the following use classifications in Chapter 17–301 of the Florida Administrative Code (i.e., identified in Section 17–302.600) are subject to the criteria in paragraph (d)(6)(ii) of this section, without exception:

Class I
Class II
Class III

(ii) The following criteria from the matrix paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(6)(i) of this section:

Use classification	Applicable criteria
Class I	This classification is assigned the criteria in: Column D1—#16
Class II Class III (marine)	This classification is assigned the criteria in:
Class III (freshwater)	This classification is assigned the criteria in: Column D2—#16

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(7) *Michigan, EPA Region 5.*

(i) All waters assigned to the following use classifications in the Michigan Department of Natural Resources Commission General Rules, R 323.1100 designated uses, as defined at R 323.1043. Definitions; A to N, (i.e., identified in Section (g) "Designated use") are subject to the criteria in paragraph (d)(7)(ii) of this section, without exception:

Agriculture
Navigation
Industrial Water Supply
Public Water Supply at the Point of Water Intake
Warmwater Fish
Other Indigenous Aquatic Life and Wildlife
Partial Body Contact Recreation

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(7)(i) of this section:

Use classification	Applicable criteria
Public Water supply	This classification is assigned the criteria in: Column B1—all, Column B2—all, Column D1—all.
All other designations	These classifications are assigned the criteria in: Column B1—all, Column B2—all, and Column D2—all.

(iii) The human health criteria shall be applied at the State-adopted 10^{-5} risk level. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(8) *Arkansas, EPA Region 6.*

(i) All waters assigned to the following use classification in section 4C (Waterbody uses) identified in Arkansas Department of Pollution Control and Ecology's Regulation No. 2 as amended and entitled, "Regulation Establishing Water Quality Standards for Surface Waters of the State of Arkansas" are subject to the criteria in paragraph (d)(8)(ii) of this section, without exception:

Extraordinary Resource Waters
Ecologically Sensitive Waterbody
Natural and Scenic Waterways
Fisheries:
(1) Trout
(2) Lakes and Reservoirs
(3) Streams
(a) Ozark Highlands Ecoregion
(b) Boston Mountains Ecoregion
(c) Arkansas River Valley Ecoregion
(d) Ouachita Mountains Ecoregion
(e) Typical Gulf Coastal Ecoregion
(f) Spring Water-influenced Gulf Coastal Ecoregion
(g) Least-altered Delta Ecoregion
(h) Channel-altered Delta Ecoregion
Domestic Water Supply

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classification identified in paragraph (d)(8)(i) of this section:

Use classification	Applicable criteria
Extraordinary Resource Waters Ecologically Sensitive Waterbody Natural and Scenic Waterways Fisheries: (1) Trout (2) Lakes and Reservoirs (3) Streams (a) Ozark Highlands Ecoregion (b) Boston Mountains Ecoregion (c) Arkansas River Valley Ecoregion (d) Ouachita Mountains Ecoregion (e) Typical Gulf Coastal Ecoregion (f) Spring Water-influenced Gulf Coastal Ecoregion (g) Least-altered Delta Ecoregion (h) Channel-altered Delta Ecoregion	These uses are each assigned the criteria in— Column B1—#4, 5a, 5b, 6, 7, 8, 9, 10, 11, 13, 14 Column B2—#4, 5a, 5b, 6 7, 8, 9, 10, 13, 14

(9) *Kansas, EPA Region 7.*

(i) All waters assigned to the following use classification in the Kansas Department of Health and Environment regulations, K.A.R. 28–16–28b through K.A.R. 28–16–28f, are subject to the criteria in paragraph (d)(9)(ii) of this section, without exception.

Section 28–16–28d
Section (2)(A)—Special Aquatic Life Use Waters
Section (2)(B)—Expected Aquatic Life Use Waters
Section (2)(C)—Restricted Aquatic Life Use Waters
Section (3)—Domestic Water Supply
Section (6)(c)—Consumptive Recreation Use.

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(9)(i) of this section:

Use classification	Applicable criteria
Sections (2)(A), (2)(B), (2)(C), (6)(C)	These classifications are each assigned all criteria in:
	Column B1, all except #9, 11, 13, 102, 105, 107, 108, 111–113, 115, 117, and 126;
	Column B2, all except #9, 13, 105, 107, 108, 111–113, 115, 117, 119–125, and 126; and
	Column D2, all except #9, 112, 113, and 115.
Section (3)	This classification is assigned all criteria in:
	Column D1, all except #9, 12, 112, 113, and 115.

(iii) The human health criteria shall be applied at the State-proposed 10^{-6} risk level.

(10) *California, EPA Region 9.*

(i) All waters assigned any aquatic life or human health use classifications in the Water Quality Control Plans for the various Basins of the State ("Basin Plans"), as amended, adopted by the California State Water Resources Control Board ("SWRCB"), except for ocean waters covered by the Water Quality Control Plan for Ocean Waters of California ("Ocean Plan") adopted by the SWRCB with resolution Number 90–27 on March 22, 1990, are subject to the criteria in paragraph (d)(10)(ii) of this section, without exception. These criteria amend the portions of the existing State standards contained in the Basin Plans. More particularly these criteria amend water quality criteria contained in the Basin Plan Chapters specifying water quality objectives (the State equivalent of federal water quality criteria) for the toxic pollutants identified in paragraph (d)(10)(ii) of this section. Although the State has adopted several use designations for each of these waters, for purposes of this action, the specific standards to be applied in paragraph (d)(10)(ii) of this section are based on the presence in all waters of some aquatic life designation and the presence or absence of the MUN use designation (Municipal and domestic supply). (See Basin Plans for more detailed use definitions.)

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the water and use classifications defined in paragraph (d)(10)(i) of this section and identified below:

Water and use classification	Applicable criteria
Waters of the State defined as bays or estuaries except the Sacramento-San Joaquin Delta and San Francisco Bay	These waters are assigned the criteria in: Column B1—pollutants 5a and 14 Column B2—pollutants 5a and 14 Column C1—pollutant 14 Column C2—pollutant 14 Column D2—pollutants 1, 12, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–44, 46, 48, 49, 54, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98
Waters of the Sacramento—San Joaquin Delta and waters of the State defined as inland (i.e., all surface waters of the State not bays or estuaries or ocean) that include a MUN use designation	These waters are assigned the criteria in: Column B1—pollutants 5a and 14 Column B2—pollutants 5a and 14 Column D1—pollutants 1, 12, 15, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–48, 49, 52, 66, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98
Waters of the State defined as inland without an MUN use designation	These waters are assigned the criteria in: Column B1—pollutants 5a and 14 Column B2—pollutants 5a and 14 Column D2—pollutants 1, 12, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–44, 46, 48, 49, 54, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98 In addition to the criteria assigned to these waters elsewhere in this rule, these waters are assigned the criteria in: Column B2—pollutant 20
Waters of the San Joaquin River from the mouth of the Merced River to Vernalis	

Water and use classification	Applicable criteria
Waters of Salt Slough, Mud Slough (north) and the San Joaquin River, Sack Dam to the mouth of the Merced River	In addition to the criteria assigned to these waters elsewhere in this rule, these waters are assigned the criteria in: Column B1—pollutant 10 Column B2—pollutant 10
Waters of San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta	These waters are assigned the criteria in: Column B1—pollutants 5a, 10* and 14 Column B2—pollutants 5a, 10* and 14 Column C1—pollutant 14 Column C2—pollutant 14 Column D2—pollutants 1, 12, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–44, 46, 48, 49, 54, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98
All inland waters of the United States or enclosed bays and estuaries that are waters of the United States that include an MUN use designation and that the State has either excluded or partially excluded from coverage under its Water Quality Control Plan for Inland Surface Waters of California, Tables 1 and 2, or its Water Quality Control Plan for Enclosed Bays and Estuaries of California, Tables 1 and 2, or has deferred applicability of those tables. (Category (a), (b), and (c) waters described on page 6 of Water Quality Control Plan for Inland Surface Waters of California or page 6 of its Water Quality Control Plan for Enclosed Bays and Estuaries of California.)	These waters are assigned the criteria for pollutants for which the State does not apply Table 1 or 2 standards. These criteria are: Column B1—all pollutants Column B2—all pollutants Column D1—all pollutants except #2
All inland waters of the United States that do not include an MUN use designation and that the State has either excluded or partially excluded from coverage under its Water Quality Control Plan for Inland Surface Waters of California, Tables 1 and 2, or has deferred applicability of these tables. (Category (a), (b), and (c) waters described on page 6 of Water Quality Control Plan for Inland Surface Waters of California.)	These waters are assigned the criteria for pollutants for which the State does not apply Table 1 or 2 standards. These criteria are: Column B1—all pollutants Column B2—all pollutants Column D2—all pollutants except #2
All enclosed bays and estuaries that are waters of the United States and that the State has either excluded or partially excluded from coverage under its Water Quality Control Plan for Inland Surface Waters of California, Tables 1 and 2, or its Water Quality Control Plan for Enclosed Bays and Estuaries of California, Tables 1 and 2, or has deferred applicability of those tables. (Category (a), (b), and (c) waters described on page 6 of Water Quality Control Plan for Inland Surface Waters of California or page 6 of its Water Quality Control Plan for Enclosed Bays and Estuaries of California.)	These waters are assigned the criteria for pollutants for which the State does not apply Table 1 or 2 standards. These criteria are: Column B1—all pollutants Column B2—all pollutants Column C1—all pollutants Column C2—all pollutants Column D2—all pollutants except #2

*The fresh water selenium criteria are included for the San Francisco Bay estuary because high levels of bioaccumulation of selenium in the estuary indicate that the salt water criteria are underprotective for San Francisco Bay.

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(11) *Nevada, EPA Region 9.* (i) All waters assigned the use classifications in Chapter 445 of the Nevada Administrative Code (NAC), Nevada Water Pollution Control Regulations, which are referred to in paragraph (d)(11)(ii) of this section, are subject to the criteria in paragraph (d)(11)(ii) of this section, without exception. These criteria amend the existing State standards contained in the Nevada Water Pollution Control Regulations. More particularly, these criteria amend or supplement the table of numeric standards in NAC 445.1339 for the toxic pollutants identified in paragraph (d)(11)(ii) of this section.

(ii) The following criteria from matrix in paragraph (b)(1) of this section apply to the waters defined in paragraph (d)(11)(i) of this section and identified below:

Water and use classification	Applicable criteria
Waters that the State has included in NAC 445.1339 where Municipal or domestic supply is a designated use	These waters are assigned the criteria in: Column B1—pollutant #118 Column B2—pollutant #118 Column D1—pollutants #15, 16, 18, 19, 20, 21, 23, 26, 27, 29, 30, 34, 37, 38, 42, 43, 55, 58–62, 64, 66, 73, 74, 78, 82, 85, 87–89, 91, 92, 96, 98, 100, 103, 104, 105, 114, 116, 117, 118
Waters that the State has included in NAC 445.1339 where Municipal or domestic supply is not a designated use	These waters are assigned the criteria in: Column B1—pollutant #118 Column B2—pollutant #118 Column D2—all pollutants except #2.

(iii) The human health criteria shall be applied at the 10^{-6} risk level, consistent with State policy. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(12) *Alaska, EPA Region 10.*

(i) All waters assigned to the following use classifications in the Alaska Administrative Code (AAC), Chapter 18 (i.e., identified in 18 AAC 70.020) are subject to the criteria in paragraph (d)(12)(ii) of this section, without exception:

70.020.(1) (A) Fresh Water
70.020.(1) (A) Water Supply
(i) Drinking, culinary, and food processing,
(iii) Aquaculture;
70.020.(1) (B) Water Recreation
(i) Contact recreation,
(ii) Secondary recreation;
70.020.(1) (C) Growth and propagation of fish, shellfish, other aquatic life, and wildlife
70.020.(2) (A) Marine Water
70.020.(2) (A) Water Supply
(i) Aquaculture,
70.020.(2) (B) Water Recreation
(i) contact recreation,
(ii) secondary recreation;
70.020.(2) (C) Growth and propagation of fish, shellfish, other aquatic life, and wildlife;
70.020.(2) (D) Harvesting for consumption of raw mollusks or other raw aquatic life.

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(12)(i) of this section:

Use classification	Applicable criteria
(1)(A) i	Column B1—all Column B2—#10 Column D1 #'s 2, 15, 16–21, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 53, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88, 89, 91–93, 96, 98, 102–105, 107–111, 117–126
(1)(A) iii	Column B1—all Column B2—#10 Column D1 #'s 2, 14, 16, 18–21, 22, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 46, 53, 54, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88–93, 95, 96, 98, 102–105, 107–111, 115–126
(1)(B)i, (1)(B) ii, (1)(C)	Column B1—all Column B2—#10 Column D2 #'s 2, 14, 16, 18–21, 22, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 46, 53, 54, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88–93, 95, 96, 98, 102–105, 107–111, 115–126
(2)(A) i, (2)(B)i, and (2)(B)ii, (2)(C), (2)(D)	Column C1—all Column C2—#10 Column D2 #s 2, 14, 16, 18–21, 22, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 46, 53, 54, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88–93, 95, 96, 98, 102–105, 107–111, 115–126

(iii) The human health criteria shall be applied at the State-proposed risk level of 10^{-5}. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(13) *Idaho, EPA Region 10.*

(i) All waters assigned to the following use classifications in the Idaho Administrative Procedures Act (IDAPA), Chapter 16 (i.e., identified in IDAPA 16.01.2100.02–16.01.2100.07) are subject to the criteria in paragraph (d)(13)(ii) of this section, without exception:

16.01.2100.01.b. Domestic Water Supplies
16.01.2100.02.a. Cold Water Biota
16.01.2100.02.b. Warm Water Biota
16.01.2100.02cc. Salmonid Spawning
16.01.2100.03.a. Primary Contact Recreation
16.01.2100.03.b Secondary Contact Recreation

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(13)(i) of this section:

Use classification	Applicable criteria
01.b	This classification is assigned the criteria in: Column D1—all *except* #14 and 115
02.a 02.b 02cc	These classifications are assigned the criteria in: Column B1—all Column B2—all Column D2—all
03.a	This classification is assigned the criteria in: Column D2—all
03.b	This classification is assigned the criteria in: Column D2—all

(iii) The human health criteria shall be applied at the 10^{-6} risk level, consistent with State policy.

(14) *Washington, EPA Region 10.*

(i) All waters assigned to the following use classifications in the Washington Administrative Code (WAC), Chapter 173–201 (i.e., identified in WAC 173–201–045) are subject to the criteria in paragraph (d)(14)(ii) of this section, without exception:

173–201–045
Fish and Shellfish
Fish
Water Supply (domestic)
Recreation

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(14)(i) of this section:

Use classification	Applicable criteria
Fish and Shellfish; Fish	These classifications are assigned the criteria in: Column B1 and B(2)—#2, 10 Column C1—#2, 10 Column C2—#2, 6, 10, 14 Column D2—all
Water Supply (domestic)	These classifications are assigned the criteria in: Column D1—all
Recreation	This classification is assigned the criteria in: Column D2—Marine waters and freshwaters not protected for domestic water supply

(iii) The human health criteria shall be applied at the State proposed risk level of 10^{-6}.

[FR Doc. 92-30611 Filed 12-21-92; 8:45 am]

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North Star Creek	Class III
Okanogan River from Reservation north boundary to Columbia River.	Class II
Olds Creek	Class I
Omak Creek	Class II
Onion Creek	Class II
Parmenter Creek	Class III
Peel Creek	Class III
Peter Dan Creek	Class III
Rock Creek	Class I
San Poil River	Class I
Sanpoil, River West Fork	Class II
Seventeen Mile Creek	Class III
Silver Creek	Class III
Sitdown Creek	Class III
Six Mile Creek	Class III
South Nanamkin Creek	Class III
Spring Creek	Class III
Stapaloop Creek	Class III
Stepstone Creek	Class III
Stranger Creek	Class II
Strawberry Creek	Class III
Swimptkin Creek	Class III
Three Forks Creek	Class I
Three Mile Creek	Class III
Thirteen Mile Creek	Class II
Thirty Mile Creek	Class II
Trail Creek	Class III
Twentyfive Mile Creek	Class III
Twentyone Mile Creek	Class III
Twentythree Mile Creek	Class III
Wannacot Creek	Class III
Wells Creek	Class I
Whitelaw Creek	Class III
Wilmont Creek	Class II
(2) Lakes:	
Apex Lake	LC
Big Goose Lake	LC
Bourgeau Lake	LC
Buffalo Lake	LC
Cody Lake	LC
Crawfish Lakes	LC
Camille Lake	LC
Elbow Lake	LC
Fish Lake	LC
Gold Lake	LC
Great Western Lake	LC
Johnson Lake	LC
LaFleur Lake	LC
Little Goose Lake	LC
Little Owhi Lake	LC
McGinnis Lake	LC
Nicholas Lake	LC
Omak Lake	SRW
Owhi Lake	SRW
Penley Lake	SRW
Rebecca Lake	LC
Round Lake	LC
Simpson Lake	LC
Soap Lake	LC
Sugar Lake	LC
Summit Lake	LC
Twin Lakes	SRW

[54 FR 28625, July 6, 1989]

§ 131.36 Toxics criteria for those states not complying with Clean Water Act section 303(c)(2)(B).

(a) *Scope.* This section is not a general promulgation of the section 304(a) criteria for priority toxic pollutants but is restricted to specific pollutants in specific States.

(b)(1) EPA's Section 304(a) criteria for Priority Toxic Pollutants.

00848

	A		B Freshwater		C Saltwater		D Human Health (10^{-6} risk for carcinogens) For consumption of:	
	(#) Compound	CAS Number	Criterion Maximum Conc.[d] (µg/L) (B1)	Criterion Continuous Conc.[d] (µg/L) (B2)	Criterion Maximum Conc.[d] (µg/L) (C1)	Criterion Continuous Conc.[d] (µg/L) (C2)	Water & Organisms (µg/L) (D1)	Organisms Only (µg/L) (D2)
1	Antimony	7440360					14 a	4300 a
2	Arsenic	7440382	360 m	190 m	69 m	36 m	0.018 abc	0.14 abc
3	Beryllium	7440417					n	n
4	Cadmium	7440439	3.7 e	1.0 e	42 m	9.3 m	n	n
5a	Chromium (III)	16065831	550 e	180 e			n	n
b	Chromium (VI)	18540299	15 m	10 m	1100 m	50 m	n	n
6	Copper	7440508	17 e	11 e	2.4 m	2.4 m		
7	Lead	7439921	65 e	2.5 e	210 m	8.1 m	n	n
8	Mercury	7439976	2.1 m	0.012 ip	1.8 m	0.025 ip	0.14	0.15
9	Nickel	7440020	1400 e	160 e	74 m	8.2 m	610 a	4600 a
10	Selenium	7782492	20 p	5 p	290 m	71 m	n	n
11	Silver	7440224	3.4 e		1.9 m			
12	Thallium	7440280					1.7 a	6.3 a
13	Zinc	7440666	110 e	100 e	90 m	81 m		
14	Cyanide	57125	22	5.2	1	1	700 a	220000 aj
15	Asbestos	1332214					7,000,000 fibers/L k	
16	2,3,7,8-TCDD (Dioxin)	1746016					0.000000014 c	
17	Acrolein	107028					320	780
18	Acrylonitrile	107131					0.059 ac	0.66 ac
19	Benzene	71432					1.2 ac	71 ac
20	Bromoform	75252					4.3 ac	360 ac
21	Carbon Tetrachloride	56235					0.25 ac	4.4 ac
22	Chlorobenzene	108907					680 a	21000 aj
23	Chlorodibromomethane	124481					0.41 ac	34 ac
24	Chloroethane	75003						
25	2-Chloroethylvinyl Ether	110758						
26	Chloroform	67663					5.7 ac	470 ac
27	Dichlorobromomethane	75274					0.27 ac	22 ac
28	1,1-Dichloroethane	75343						
29	1,2-Dichloroethane	107062					0.38 ac	99 ac
30	1,1-Dichloroethylene	75354					0.057 ac	3.2 ac
31	1,2-Dichloropropane	78875						
32	1,3-Dichloropropylene	542756					10 a	1700 a
33	Ethylbenzene	100414					3100 a	29000 a
34	Methyl Bromide	74839					48 a	4000 a
35	Methyl Chloride	74873					n	n
36	Methylene Chloride	75092					4.7 ac	1600 ac
37	1,1,2,2-Tetrachloroethane	79345					0.17 ac	11 ac
38	Tetrachloroethylene	127184					0.8 c	8.85 c
39	Toluene	108883					6800 a	200000 a

00849

40	1,2-Trans-Dichloroethylene	156605					n	n
41	1,1,1-Trichloroethane	71556					0.60 ac	42 ac
42	1,1,2-Trichloroethane	79005					2.7 c	81 c
43	Trichloroethylene	79016					2 c	525 c
44	Vinyl Chloride	75014						
45	2-Chlorophenol	95578					93 a	790 aj
46	2,4-Dichlorophenol	120832						
47	2,4-Dimethylphenol	105679					13.4	765
48	2-Methyl-4,6-Dinitrophenol	534521					70 a	14000 a
49	2,4-Dinitrophenol	51285						
50	2-Nitrophenol	88755						
51	4-Nitrophenol	100027						
52	3-Methyl-4-Chlorophenol	59507				7.9	0.28 ac	8.2 acj
53	Pentachlorophenol	87865	20 f	13 f	13		21000 a	4600000 aj
54	Phenol	108952					2.1 ac	6.5 ac
55	2,4,6-Trichlorophenol	88062						
56	Acenaphthene	83329						
57	Acenaphthylene	208968						
58	Anthracene	120127					9600 a	110000 a
59	Benzidine	92875					0.00012 ac	0.00054 ac
60	Benzo(a)Anthracene	56553					0.0028 c	0.031 c
61	Benzo(a)Pyrene	50328					0.0028 c	0.031 c
62	Benzo(b)Fluoranthene	205992					0.0028 c	0.031 c
63	Benzo(ghi)Perylene	191242						
64	Benzo(k)Fluoranthene	207089					0.0028 c	0.031 c
65	Bis(2-Chloroethoxy)Methane	111911						
66	Bis(2-Chloroethyl)Ether	111444					0.031 ac	1.4 ac
67	Bis(2-Chloroisopropyl)Ether	108601					1400 a	170000 a
68	Bis(2-Ethylhexyl)Phthalate	117817					1.8 ac	5.9 ac
69	4-Bromophenyl Phenyl Ether	101553						
70	Butylbenzyl Phthalate	85687						
71	2-Chloronaphthalene	91587						
72	4-Chlorophenyl Phenyl Ether	7005723						
73	Chrysene	218019					0.0028 c	0.031 c
74	Dibenzo(ah)Anthracene	53703					0.0028 c	0.031 c
75	1,2-Dichlorobenzene	95501					2700 a	17000 a
76	1,3-Dichlorobenzene	541731					400	2600
77	1,4-Dichlorobenzene	106467					400	2600
78	3,3'-Dichlorobenzidine	91941					0.04 ac	0.077 ac
79	Diethyl Phthalate	84662					23000 a	120000 a
80	Dimethyl Phthalate	131113					313000	2900000
81	Di-n-Butyl Phthalate	84742					2700 a	12000 a
82	2,4-Dinitrotoluene	121142					0.11 c	9.1 c
83	2,6-Dinitrotoluene	606202						
84	Di-n-Octyl Phthalate	117840						
85	1,2-Diphenylhydrazine	122667					0.040 ac	0.54 ac
86	Fluoranthene	206440					300 a	370 a
87	Fluorene	86737					1300 a	14000 a
88	Hexachlorobenzene	118741					0.00075 ac	0.00077 ac
89	Hexachlorobutadiene	87683					0.44 ac	50 ac

A			B Freshwater		C Saltwater		D Human Health (10^{-6} risk for carcinogens) For consumption of:	
(#) Compound	CAS Number		Criterion Maximum Conc.[d] (µg/L) (B1)	Criterion Continuous Conc.[d] (µg/L) (B2)	Criterion Maximum Conc.[d] (µg/L) (C1)	Criterion Continuous Conc.[d] (µg/L) (C2)	Water & Organisms (µg/L) (D1)	Organisms Only (µg/L) (D2)
90	Hexachlorocyclopentadiene	77474					240 a	17000 aj
91	Hexachloroethane	67721					1.9 ac	8.9 ac
92	Indeno(1,2,3-cd)Pyrene	193395					0.0028 c	0.031 c
93	Isophorone	78591					8.4 ac	600 ac
94	Naphthalene	91203						
95	Nitrobenzene	98953					17 a	1900 aj
96	N-Nitrosodimethylamine	62759					0.00069 ac	8.1 ac
97	N-Nitrosodi-n-Propylamine	621647						
98	N-Nitrosodiphenylamine	86306					5.0 ac	16 ac
99	Phenanthrene	85018						
100	Pyrene	129000					960 a	11000 a
101	1,2,4-Trichlorobenzene	120821						
102	Aldrin	309002	3 g		1.3 g		0.00013 ac	0.00014 ac
103	alpha-BHC	319846					0.0039 ac	0.013 ac
104	beta-BHC	319857					0.014 ac	0.046 ac
105	gamma-BHC	58899	2 g	0.08 g	0.16 g		0.019 c	0.063 c
106	delta-BHC	319868						
107	Chlordane	57749	2.4 g	0.0043 g	0.09 g	0.004 g	0.00057 ac	0.00059 ac
108	4,4'-DDT	50293	1.1 g	0.001 g	0.13 g	0.001 g	0.00059 ac	0.00059 ac
109	4,4'-DDE	72559					0.00059 ac	0.00059 ac
110	4,4'-DDD	72548					0.00083 ac	0.00084 ac
111	Dieldrin	60571	2.5 g	0.0019 g	0.71 g	0.0019 g	0.00014 ac	0.00014 ac
112	alpha-Endosulfan	959988	0.22 g	0.056 g	0.034 g	0.0087 g	0.93 a	2.0 a
113	beta-Endosulfan	33213659	0.22 g	0.056 g	0.034 g	0.0087 g	0.93 a	2.0 a
114	Endosulfan Sulfate	1031078					0.93 a	2.0 a
115	Endrin	72208	0.18 g	0.0023 g	0.037 g	0.0023 g	0.76 a	0.81 aj
116	Endrin Aldehyde	7421934					0.76 a	0.81 aj
117	Heptachlor	76448	0.52 g	0.0038 g	0.053 g	0.0036 g	0.00021 ac	0.00021 ac
118	Heptachlor Epoxide	1024573	0.52 g	0.0038 g	0.053 g	0.0036 g	0.00010 ac	0.00011 ac
119	PCB–1242	53469219		0.014 g		0.03 g		
120	PCB–1254	11097691		0.014 g		0.03 g		
121	PCB–1221	11104282		0.014 g		0.03 g		
122	PCB–1232	11141165		0.014 g		0.03 g		
123	PCB–1248	12672296		0.014 g		0.03 g		
124	PCB–1260	11096825		0.014 g		0.03 g		
125a	PCB–1016	12674112		0.014 g		0.03 g		
125b	Polychlorinated biphenyls (PCBs)						0.00017 q	0.00017 q
126	Toxaphene	8001352	0.73	0.0002	0.21	0.0002	0.00073 ac	0.00075 ac
	Total Number of Criteria (h) =		24	29	23	27	85	84

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FOOTNOTES

a. Criteria revised to reflect current agency q_1* or RfD, as contained in the Integrated Risk Information System (IRIS). The fish tissue bioconcentration factor (BCF) from the 1980 criteria documents was retained in all cases.

b. The criteria refers to the inorganic form only.

c. Criteria in the matrix based on carcinogenicity (10^{-6} risk). For a risk level of 10^{-5}, move the decimal point in the matrix value one place to the right.

d. Criteria Maximum Concentration (CMC) = the highest concentration of a pollutant to which aquatic life can be exposed for a short period of time (1-hour average) without deleterious effects. Criteria Continuous Concentration (CCC) = the highest concentration of a pollutant to which aquatic life can be exposed for an extended period of time (4 days) without deleterious effects. µg/L = micrograms per liter.

e. Freshwater aquatic life criteria for these metals are expressed as a function of total hardness (mg/L as $CaCO_3$), the pollutant's water effect ratio (WER) as defined in §131.36(c) and multiplied by an appropriate dissolved conversion factor as defined in §131.36(b)(2). For comparative purposes, the values displayed in this matrix are shown as dissolved metal and correspond to a total hardness of 100 mg/L and a water effect ratio of 1.0.

f. Freshwater aquatic life criteria for pentachlorophenol are expressed as a function of pH, and are calculated as follows. Values displayed above in the matrix correspond to a pH of 7.8.

$$CMC = \exp(1.005(pH) - 4.830)$$
$$CCC = \exp(1.005(pH) - 5.290)$$

g. Aquatic life criteria for these compounds were issued in 1980 utilizing the 1980 Guidelines for criteria development. The acute values shown are final acute values (FAV) which by the 1980 Guidelines are instantaneous values as contrasted with a CMC which is a one-hour average.

h. These totals simply sum the criteria in each column. For aquatic life, there are 31 priority toxic pollutants with some type of freshwater or saltwater, acute or chronic criteria. For human health, there are 85 priority toxic pollutants with either ''water + fish'' or ''fish only'' criteria. Note that these totals count chromium as one pollutant even though EPA has developed criteria based on two valence states. In the matrix, EPA has assigned numbers 5a and 5b to the criteria for chromium to reflect the fact that the list of 126 priority toxic pollutants includes only a single listing for chromium.

i. If the CCC for total mercury exceeds 0.012 µg/l more than once in a 3-year period in the ambient water, the edible portion of aquatic species of concern must be analyzed to determine whether the concentration of methyl mercury exceeds the FDA action level (1.0 mg/kg). If the FDA action level is exceeded, the State must notify the appropriate EPA Regional Administrator, initiate a revision of its mercury criterion in its water quality standards so as to protect designated uses, and take other appropriate action such as issuance of a fish consumption advisory for the affected area.

j. No criteria for protection of human health from consumption of aquatic organisms (excluding water) was presented in the 1980 criteria document or in the 1986 Quality Criteria for Water. Nevertheless, sufficient information was presented in the 1980 document to allow a calculation of a criterion, even though the results of such a calculation were not shown in the document.

k. The criterion for asbestos is the MCL (56 FR 3526, January 30, 1991).

l. [Reserved: This letter not used as a footnote.]

m. Criteria for these metals are expressed as a function of the water effect ratio, WER, as defined in 40 CFR 131.36(c).

CMC = column B1 or C1 value × WER
CCC = column B2 or C2 value × WER

n. EPA is not promulgating human health criteria for this contaminant. However, permit authorities should address this contaminant in NPDES permit actions using the State's existing narrative criteria for toxics.

o. [Reserved: This letter not used as a footnote.]

p. Criterion expressed as total recoverable.

q. This criterion applies to total PCBs (*e.g.*, the sum of all congener or isomer or homolog or Aroclor analyses).

GENERAL NOTES

1. This chart lists all of EPA's priority toxic pollutants whether or not criteria recommendations are available. Blank spaces indicate the absence of criteria recommendations. Because of variations in chemical nomenclature systems, this listing of toxic pollutants does not duplicate the listing in Appendix A of 40 CFR Part 423. EPA has added the Chemical Abstracts Service (CAS) registry numbers, which provide a unique identification for each chemical.

2. The following chemicals have organoleptic based criteria recommendations that are not included on this chart (for reasons which are discussed in the preamble): copper, zinc, chlorobenzene, 2-chlorophenol, 2,4-dichlorophenol, acenaphthene, 2,4-dimethylphenol, 3-methyl-4-chlorophenol, hexachlorocyclopentadiene, pentachlorophenol, phenol.

3. For purposes of this rulemaking, freshwater criteria and saltwater criteria apply as specified in 40 CFR 131.36(c).

NOTE TO PARAGRAPH (b)(1): On April 14, 1995, the Environmental Protection Agency

issued a stay of certain criteria in paragraph (b)(1) of this section as follows: the criteria in columns B and C for arsenic, cadmium, chromium (VI), copper, lead, nickel, silver, and zinc; the criteria in B1 and C1 for mercury; the criteria in column B for chromium (III); and the criteria in column C for selenium. The stay remains in effect until further notice.

(2) Factors for Calculating Hardness-Dependent, Freshwater Metals Criteria

CMC=WER exp { m_A[ln(hardness)]+b_A} × Acute Conversion Factor

CCC=WER exp { m_C[ln(hardness)]+b_C} × Chronic Conversion Factor

Final CMC and CCC values should be rounded to two significant figures.

Metal	m_A	b_A	m_C	b_C	Freshwater conversion factors	
					Acute	Chronic
Cadmium	1.128	–3.828	0.7852	–3.490	[a] 0.944	[a] 0.909
Chromium (III)	0.8190	3.688	0.8190	1.561	0.316	0.860
Copper	0.9422	–1.464	0.8545	–1.465	0.960	0.960
Lead	1.273	-1.460	1.273	–4.705	[a] 0.791	[a] 0.791
Nickel	0.8460	3.3612	0.8460	1.1645	0.998	0.997
Silver	1.72	–6.52	[b] N/A	[b] N/A	0.85	[b] N/A
Zinc	0.8473	0.8604	0.8473	0.7614	0.978	0.986

Note to table: The term ''exp'' represents the base e exponential function.

Footnotes to table:

[a] The freshwater conversion factors (CF) for cadmium and lead are hardness-dependent and can be calculated for any hardness [see limitations in § 131.36(c)(4)] using the following equations:

Cadmium
Acute: CF=1.136672—[(ln hardness)(0.041838)]
Chronic: CF=1.101672—[(ln hardness)(0.041838)]
Lead (Acute and Chronic): CF = 1.46203—[(ln hardness)(0.145712)]

[b] No chronic criteria are available for silver.

(c) *Applicability*. (1) The criteria in paragraph (b) of this section apply to the States' designated uses cited in paragraph (d) of this section and supersede any criteria adopted by the State, except when State regulations contain criteria which are more stringent for a particular use in which case the State's criteria will continue to apply.

(2) The criteria established in this section are subject to the State's general rules of applicability in the same way and to the same extent as are the other numeric toxics criteria when applied to the same use classifications including mixing zones, and low flow values below which numeric standards can be exceeded in flowing fresh waters.

(i) For all waters with mixing zone regulations or implementation procedures, the criteria apply at the appropriate locations within or at the boundary of the mixing zones; otherwise the criteria apply throughout the waterbody including at the end of any discharge pipe, canal or other discharge point.

(ii) A State shall not use a low flow value below which numeric standards can be exceeded that is less stringent than the following for waters suitable for the establishment of low flow return frequencies (i.e., streams and rivers):

AQUATIC LIFE	
Acute criteria (CMC)	1 Q 10 or 1 B 3
Chronic criteria (CCC)	7 Q 10 or 4 B 3
HUMAN HEALTH	
Non-carcinogens	30 Q 5
Carcinogens	Harmonic mean flow

Where:

CMC—criteria maximum concentration—the water quality criteria to protect against acute effects in aquatic life and is the highest instream concentration of a priority toxic pollutant consisting of a one-hour average not to be exceeded more than once every three years on the average;

CCC—criteria continuous concentration—the water quality criteria to protect against chronic effects in aquatic life is the highest instream concentration of a priority toxic pollutant consisting of a 4-day average not to be exceeded more than once every three years on the average;

1 Q 10 is the lowest one day flow with an average recurrence frequency of once in 10 years determined hydrologically;

1 B 3 is biologically based and indicates an allowable exceedence of once every 3 years. It is determined by EPA's computerized method (DFLOW model);

7 Q 10 is the lowest average 7 consecutive day low flow with an average recurrence frequency of once in 10 years determined hydrologically;

4 B 3 is biologically based and indicates an allowable exceedence for 4 consecutive days once every 3 years. It is determined by EPA's computerized method (DFLOW model);

30 Q 5 is the lowest average 30 consecutive day low flow with an average recurrence frequency of once in 5 years determined hydrologically; and the harmonic mean

flow is a long term mean flow value calculated by dividing the number of daily flows analyzed by the sum of the reciprocals of those daily flows.

(iii) If a State does not have such a low flow value for numeric standards compliance, then none shall apply and the criteria included in paragraph (d) of this section herein apply at all flows.

(3) The aquatic life criteria in the matrix in paragraph (b) of this section apply as follows:

(i) For waters in which the salinity is equal to or less than 1 part per thousand 95% or more of the time, the applicable criteria are the freshwater criteria in Column B;

(ii) For waters in which the salinity is equal to or greater than 10 parts per thousand 95% or more of the time, the applicable criteria are the saltwater criteria in Column C; and

(iii) For waters in which the salinity is between 1 and 10 parts per thousand as defined in paragraphs (c)(3) (i) and (ii) of this section, the applicable criteria are the more stringent of the freshwater or saltwater criteria. However, the Regional Administrator may approve the use of the alternative freshwater or saltwater criteria if scientifically defensible information and data demonstrate that on a site-specific basis the biology of the waterbody is dominated by freshwater aquatic life and that freshwater criteria are more appropriate; or conversely, the biology of the waterbody is dominated by saltwater aquatic life and that saltwater criteria are more appropriate.

(4) *Application of metals criteria.* (i) For purposes of calculating freshwater aquatic life criteria for metals from the equations in paragraph (b)(2) of this section, the minimum hardness allowed for use in those equations shall not be less than 25 mg/l, as calcium carbonate, even if the actual ambient hardness is less than 25 mg/l as calcium carbonate. The maximum hardness value for use in those equations shall not exceed 400 mg/l as calcium carbonate, even if the actual ambient hardness is greater than 400 mg/l as calcium carbonate. The same provisions apply for calculating the metals criteria for the comparisons provided for in paragraph (c)(3)(iii) of this section.

(ii) The hardness values used shall be consistent with the design discharge conditions established in paragraph (c)(2) of this section for flows and mixing zones.

(iii) Except where otherwise noted, the criteria for metals (compounds #2, #4–# 11, and #13, in paragraph (b) of this section) are expressed as dissolved metal. For purposes of calculating aquatic life criteria for metals from the equations in footnote m. in the criteria matrix in paragraph (b)(1) of this section and the equations in paragraphs (b)(2) of this section, the water-effect ratio is computed as a specific pollutant's acute or chronic toxicity values measured in water from the site covered by the standard, divided by the respective acute or chronic toxicity value in laboratory dilution water.

(d) *Criteria for Specific Jurisdictions—*(1) *Rhode Island, EPA Region 1.* (i) All waters assigned to the following use classifications in the Water Quality Regulations for Water Pollution Control adopted under Chapters 46–12, 42–17.1, and 42–35 of the General Laws of Rhode Island are subject to the criteria in paragraph (d)(1)(ii) of this section, without exception:

6.21 Freshwater	6.22 Saltwater:
Class A	Class SA
Class B	Class SB
Class C	Class SC

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(1)(i) of this section:

Use classification	Applicable criteria
Class A Class B waters where water supply use is designated Class B waters where water supply use is not designated. Class C; Class SA; Class SB; Class SC	These classifications are assigned the criteria in Column D1—#2, 68 Each of these classifications is assigned the criteria in: Column D2—#2, 68

(iii) The human health criteria shall be applied at the 10^{-5} risk level, consistent with the State policy. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(2) *Vermont, EPA Region 1.* (i) All waters assigned to the following use classifications in the Vermont Water Quality Standards adopted under the authority of the Vermont Water Pollution Control Act (10 V.S.A., Chapter 47) are subject to the criteria in paragraph (d)(2)(ii) of this section, without exception:

Class A
Class B
Class C

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(2)(i) of this section:

Use classification	Applicable criteria
1. Classes A1, A2, B1, B2, B3	These classification are assigned the criterion in: Column B2—#105.

(iii) The human health criteria shall be applied at the State-proposed 10^{-6} risk level.

(3) *New Jersey, EPA Region 2.* (i) All waters assigned to the following use classifications in the New Jersey Administrative Code (N.J.A.C.) 7:9–4.1 et seq., Surface Water Quality Standards, are subject to the criteria in paragraph (d)(3)(ii) of this section, without exception.

N.J.A.C. 7:9–4.12(b): Class PL
N.J.A.C. 7:9–4.12(c): Class FW2
N.J.A.C. 7:9–4.12(d): Class SE1
N.J.A.C. 7:9–4.12(e): Class SE2
N.J.A.C. 7:9–4.12(f): Class SE3
N.J.A.C. 7:9–4.12(g): Class SC
N.J.A.C. 7:9–4.13(a): Delaware River Zones 1C, 1D, and 1E
N.J.A.C. 7:9–4.13(b): Delaware River Zone 2
N.J.A.C. 7:9–4.13(c): Delaware River Zone 3
N.J.A.C. 7:9–4.13(d): Delaware River Zone 4
N.J.A.C. 7:9–4.13(e): Delaware River Zone 5
N.J.A.C. 7:9–4.13(f): Delaware River Zone 6

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(3)(i) of this section:

Use classification	Applicable criteria
1. Freshwater Pinelands, FW2	These classifications are each assigned the criteria in: i. Column B1—#2, 4, 5a, 5b, 6–11, 13. ii. Column B2—#2, 4, 5a, 5b, 6–10, 13. iii. Column D1—#125b at a 10^{-6} risk level. iv. Column D2—#125b at a 10^{-6} risk level. v. Column D2—#23, 30, 37, 42, 87, 89, 93 and 105 at a 10^{-5} risk level.
2. PL (Saline Water Pinelands), SE1, SE2, SE3, SC, Delaware Bay Zone 6.	These classifications are each assigned the criteria in: i. Column C1—#2, 4, 5b, 6–11, 13. ii. Column C2—#2, 4, 5b, 6–10, 13. iii. Column D1—#125b at a 10^{-6} risk level. iv. Column D2—#125b at a 10^{-6} risk level. v. Column D2—#23, 30, 37, 42, 87, 89, 93 and 105 at a 10^{-5} risk level.
3. Delaware River Zones 1C, 1D, 1E, 2, 3, 4, and 5	i. Column B1—none. ii. Column B2—none. iii. Column D1—none. iv. Column D2—none.
4. Delaware River Zones 3, 4, and 5	These classifications are each assigned the criteria in: i. Column C1—none. ii. Column C2—none. iii. Column D2—none.

(iii) The human health criteria shall be applied at the State-proposed 10^{-6} risk level for EPA rated Class A, B_1, and B_2 carcinogens; EPA rated Class C carcinogens shall be applied at 10^{-5} risk level. To determine appropriate value for carcinogens, see footnote c. in the matrix in paragraph (b)(1) of this section.

(4) *Puerto Rico, EPA Region 2.* (i) All waters assigned to the following use classifications in the Puerto Rico

Water Quality Standards (promulgated by Resolution Number R–83–5–2) are subject to the criteria in paragraph (d)(4)(ii) of this section, without exception.

Article 2.2.2—Class SB
Article 2.2.3—Class SC
Article 2.2.4—Class SD

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(4)(i) of this section:

Use classification	Applicable criteria
Class SD	Column B1—# 118. Column B2—#s 8, 105, 115, 118, 119, 120, 121, 122, 123,124, 125a, 125b. Column D1—#s 12, 16, 27, 60, 61, 62, 64, 73, 74, 92, 93, 103, 104, 114, 116, 118, 119, 120, 121, 122, 123, 124, 125a, 125b.
Class SB, Class SC	Column C1—#s 5b, 112, 113, 118. Column C2—#s 5b, 8, 112, 113, 118, 119, 120, 121, 122, 123, 124, 125a, 125b. Column D2—#s 12, 16, 27, 60, 61, 62, 64, 73, 74, 87, 92, 93, 103, 104, 114, 116, 118, 119, 120, 121, 122, 123, 124, 125a, 125b.

(iii) The human health criteria shall be applied at the State-proposed 10^{-5} risk level. To determine appropriate value for carcinogens, see footnote c, in the criteria matrix in paragraph (b)(1) of this section.

(5) *District of Columbia, EPA Region 3.* (i) All waters assigned to the following use classifications in chapter 11 Title 21 DCMR, Water Quality Standards of the District of Columbia are subject to the criteria in paragraph (d)(5)(ii) of this section, without exception:

1101.2 Class C waters

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classification identified in paragraph (d)(5)(i) of this section:

Use classification	Applicable criteria
1. Class C	This classification is assigned the additional criteria in: Column B2; #10, 118, 126.

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(6) *Florida, EPA Region 4.* (i) All waters assigned to the following use classifications in Chapter 17–301 of the Florida Administrative Code (i.e., identified in Section 17–302.600) are subject to the criteria in paragraph (d)(6)(ii) of this section, without exception:

Class I
Class II
Class III

(ii) The following criteria from the matrix paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(6)(i) of this section:

Use classification	Applicable criteria
Class I	This classification is assigned the criteria in: Column D1—#16
Class II	This classification is assigned the criteria in:
Class III (marine)	Column D2—#16
Class III (freshwater)	This classification is assigned the criteria in: Column D2—#16

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(7)–(8) [Reserved]

(9) *Kansas, EPA Region 7.* (i) All waters assigned to the following use classification in the Kansas Department of Health and Environment regulations, K.A.R. 28–16–28b through K.A.R. 28–16–28f, are subject to the criteria in paragraph (d)(9)(ii) of this section, without exception.

Section (2)(A)—Special Aquatic Life Use Waters
Section (2)(B)—Expected Aquatic Life Use Waters
Section (2)(C)—Restricted Aquatic Life Use Waters
Section (3)—Domestic Water Supply.
Section (4)—Food Procurement Use.

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(9)(i) of this section:

Use classification	Applicable criteria
1. Sections (2)(A), (2)(B), (2)(C), (4)	These classifications are each assigned criteria as follows: i. Column B1, #2. ii. Column D2, #12, 21, 29, 39, 46, 68, 79, 81, 86, 93, 104, 114, 118.
2. Section (3)	This classification is assigned all criteria in: Column D1, all except #1, 9, 12, 14, 15, 17, 22, 33, 36, 39, 44, 75, 77, 79, 90, 112, 113, and 115.

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(10) *California, EPA Region 9.* (i) All waters assigned any aquatic life or human health use classifications in the Water Quality Control Plans for the various Basins of the State (''Basin Plans''), as amended, adopted by the California State Water Resources Control Board (''SWRCB''), except for ocean waters covered by the Water Quality Control Plan for Ocean Waters of California (''Ocean Plan'') adopted by the SWRCB with resolution Number 90–27 on March 22, 1990, are subject to the criteria in paragraph (d)(10)(ii) of this section, without exception. These criteria amend the portions of the existing State standards contained in the Basin Plans. More particularly these criteria amend water quality criteria contained in the Basin Plan Chapters specifying water quality objectives (the State equivalent of federal water quality criteria) for the toxic pollutants identified in paragraph (d)(10)(ii) of this section. Although the State has adopted several use designations for each of these waters, for purposes of this action, the specific standards to be applied in paragraph (d)(10)(ii) of this section are based on the presence in all waters of some aquatic life designation and the presence or absence of the MUN use designation (Municipal and domestic supply). (See Basin Plans for more detailed use definitions.)

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the water and use classifications defined in paragraph (d)(10)(i) of this section and identified below:

Water and use classification	Applicable criteria
Waters of the State defined as bays or estuaries except the Sacramento-San Joaquin Delta and San Francisco Bay	These waters are assigned the criteria in: Column B1—pollutants 5a and 14 Column B2—pollutants 5a and 14 Column C1—pollutant 14 Column C2—pollutant 14 Column D2—pollutants 1, 12, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–44, 46, 48, 49, 54, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98

Water and use classification	Applicable criteria
Waters of the Sacramento—San Joaquin Delta and waters of the State defined as inland (i.e., all surface waters of the State not bays or estuaries or ocean) that include a MUN use designation	These waters are assigned the criteria in: Column B1—pollutants 5a and 14 Column B2—pollutants 5a and 14 Column D1—pollutants 1, 12, 15, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–48, 49, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98
Waters of the State defined as inland without an MUN use designation	These waters are assigned the criteria in: Column B1—pollutants 5a and 14 Column B2—pollutants 5a and 14 Column D2—pollutants 1, 12, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–44, 46, 48, 49, 54, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98
Waters of the San Joaquin River from the mouth of the Merced River to Vernalis	In addition to the criteria assigned to these waters elsewhere in this rule, these waters are assigned the criteria in: Column B2—pollutant 10
Waters of Salt Slough, Mud Slough (north) and the San Joaquin River, Sack Dam to the mouth of the Merced River	In addition to the criteria assigned to these waters elsewhere in this rule, these waters are assigned the criteria in: Column B1—pollutant 10 Column B2—pollutant 10
Waters of San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta	These waters are assigned the criteria in: Column B1—pollutants 5a, 10* and 14 Column B2—pollutants 5a, 10* and 14 Column C1—pollutant 14 Column C2—pollutant 14 Column D2—pollutants 1, 12, 17, 18, 21, 22, 29, 30, 32, 33, 37, 38, 42–44, 46, 48, 49, 54, 59, 66, 67, 68, 78–82, 85, 89, 90, 91, 93, 95, 96, 98
All inland waters of the United States or enclosed bays and estuaries that are waters of the United States that include an MUN use designation and that the State has either excluded or partially excluded from coverage under its Water Quality Control Plan for Inland Surface Waters of California, Tables 1 and 2, or its Water Quality Control Plan for Enclosed Bays and Estuaries of California, Tables 1 and 2, or has deferred applicability of those tables. (Category (a), (b), and (c) waters described on page 6 of Water Quality Control Plan for Inland Surface Waters of California or page 6 of its Water Quality Control Plan for Enclosed Bays and Estuaries of California.)	These waters are assigned the criteria for pollutants for which the State does not apply Table 1 or 2 standards. These criteria are: Column B1—all pollutants Column B2—all pollutants Column D1—all pollutants except #2

Water and use classification	Applicable criteria
All inland waters of the United States that do not include an MUN use designation and that the State has either excluded or partially excluded from coverage under its Water Quality Control Plan for Inland Surface Waters of California, Tables 1 and 2, or has deferred applicability of these tables. (Category (a), (b), and (c) waters described on page 6 of Water Quality Control Plan for Inland Surface Waters of California.)	These waters are assigned the criteria for pollutants for which the State does not apply Table 1 or 2 standards. These criteria are: Column B1—all pollutants Column B2—all pollutants Column D2—all pollutants except #2
All enclosed bays and estuaries that are waters of the United States that do not include an MUN designation and that the State has either excluded or partially excluded from coverage under its Water Quality Control Plan for Inland Surface Waters of California, Tables 1 and 2, or its Water Quality Control Plan for Enclosed Bays and Estuaries of California, Tables 1 and 2, or has deferred applicability of those tables. (Category (a), (b), and (c) waters described on page 6 of Water Quality Control Plan for Inland Surface Waters of California or page 6 of its Water Quality Control Plan for Enclosed Bays and Estuaries of California.)	These waters are assigned the criteria for pollutants for which the State does not apply Table 1 or 2 standards. These criteria are: Column B1—all pollutants Column B2—all pollutants Column C1—all pollutants Column C2—all pollutants Column D2—all pollutants except #2

*The fresh water selenium criteria are included for the San Francisco Bay estuary because high levels of bioaccumulation of selenium in the estuary indicate that the salt water criteria are underprotective for San Francisco Bay.

(iii) The human health criteria shall be applied at the State-adopted 10^{-6} risk level.

(11) *Nevada, EPA Region 9.* (i) All waters assigned the use classifications in Chapter 445 of the Nevada Administrative Code (NAC), Nevada Water Pollution Control Regulations, which are referred to in paragraph (d)(11)(ii) of this section, are subject to the criteria in paragraph (d)(11)(ii) of this section, without exception. These criteria amend the existing State standards contained in the Nevada Water Pollution Control Regulations. More particularly, these criteria amend or supplement the table of numeric standards in NAC 445.1339 for the toxic pollutants identified in paragraph (d)(11)(ii) of this section.

(ii) The following criteria from matrix in paragraph (b)(1) of this section apply to the waters defined in paragraph (d)(11)(i) of this section and identified below:

Water and use classification	Applicable criteria
Waters that the State has included in NAC 445.1339 where Municipal or domestic supply is a designated use	These waters are assigned the criteria in: Column B1—pollutant #118 Column B2—pollutant #118 Column D1—pollutants #15, 16, 18, 19, 20, 21, 23, 26, 27, 29, 30, 34, 37, 38, 42, 43, 55, 58–62, 64, 66, 73, 74, 78, 82, 85, 87–89, 91, 92, 96, 98, 100, 103, 104, 105, 114, 116, 117, 118
Waters that the State has included in NAC 445.1339 where Municipal or domestic supply is not a designated use	These waters are assigned the criteria in: Column B1—pollutant #118 Column B2—pollutant #118 Column D2—all pollutants except #2.

(iii) The human health criteria shall be applied at the 10^{-5} risk level, consistent with State policy. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(12) *Alaska, EPA Region 10.* (i) All waters assigned to the following use classifications in the Alaska Administrative Code (AAC), Chapter 18 (i.e., identified in 18 AAC 70.020) are subject to the criteria in paragraph (d)(12)(ii) of this section, without exception:

00859

70.020.(1) (A) Fresh Water
70.020.(1) (A) Water Supply
(i) Drinking, culinary, and food processing,
(iii) Aquaculture;
70.020.(1) (B) Water Recreation
(i) Contact recreation,
(ii) Secondary recreation;
70.020.(1) (C) Growth and propagation of fish, shellfish, other aquatic life, and wildlife
70.020.(2) (A) Marine Water
70.020.(2) (A) Water Supply
(i) Aquaculture,
70.020.(2) (B) Water Recreation
(i) contact recreation,
(ii) secondary recreation;
70.020.(2) (C) Growth and propagation of fish, shellfish, other aquatic life, and wildlife;
70.020.(2) (D) Harvesting for consumption of raw mollusks or other raw aquatic life.

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(12)(i) of this section:

Use classification	Applicable criteria
(1)(A)(i)	Column D1—#s 16, 18–21, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 53, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88, 89, 91–93, 96, 98, 102–105, 107–111, 117–126.
(1)(A)(iii)	Column D2—#s 14, 16, 18–21, 22, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 46, 53, 54, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88–93, 95, 96, 98, 102–105, 107–111, 115–126.
(1)(B)(i), (1)(B)(ii), (1)(C)	Column D2—#s 14, 16, 18–21, 22, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 46, 53, 54, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88–93, 95, 96, 98, 102–105, 107–111, 115–126.
(2)(A)(i), (2)(B)(i), and (2)(B)ii, (2)(C), (2)(D)	Column D2—#s 14, 16, 18–21, 22, 23, 26, 27, 29, 30, 32, 37, 38, 42–44, 46, 53, 54, 55, 59–62, 64, 66, 68, 73, 74, 78, 82, 85, 88–93, 95, 96, 98, 102–105, 107–111, 115–126.

(iii) The human health criteria shall be applied at the State-proposed risk level of 10^{-5}. To determine appropriate value for carcinogens, see footnote c in the criteria matrix in paragraph (b)(1) of this section.

(13) [Reserved]

(14) *Washington, EPA Region 10.* (i) All waters assigned to the following use classifications in the Washington Administrative Code (WAC), Chapter 173–201 (i.e., identified in WAC 173–201–045) are subject to the criteria in paragraph (d)(14)(ii) of this section, without exception:

173–201–045
Fish and Shellfish
Fish
Water Supply (domestic)
Recreation

(ii) The following criteria from the matrix in paragraph (b)(1) of this section apply to the use classifications identified in paragraph (d)(14)(i) of this section:

Use classification	Applicable criteria
Fish and Shellfish; Fish	These classifications are assigned the criteria in: Column D2—all.
Water Supply (domestic)	These classifications are assigned the criteria in: Column D1—all.
Recreation	This classification is assigned the criteria in: Column D2—Marine waters and freshwaters not protected for domestic water supply.

(iii) The human health criteria shall be applied at the State proposed risk level of 10^{-6}.

[57 FR 60910, Dec. 22, 1992]

EDITORIAL NOTE: For FEDERAL REGISTER citations affecting §131.36, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and on GPO Access.

§131.37 California.

(a) *Additional criteria.* The following criteria are applicable to waters specified in the Water Quality Control Plan for Salinity for the San Francisco Bay/Sacramento-San Joaquin Delta Estuary, adopted by the California State Water Resources Control Board in State Board Resolution No. 91–34 on May 1, 1991:

00860

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 131

[FRL–6587–9]

RIN 2040–AC44

Water Quality Standards; Establishment of Numeric Criteria for Priority Toxic Pollutants for the State of California

AGENCY: Environmental Protection Agency.

ACTION: Final rule.

SUMMARY: This final rule promulgates: numeric aquatic life criteria for 23 priority toxic pollutants; numeric human health criteria for 57 priority toxic pollutants; and a compliance schedule provision which authorizes the State to issue schedules of compliance for new or revised National Pollutant Discharge Elimination System permit limits based on the federal criteria when certain conditions are met.

EPA is promulgating this rule based on the Administrator's determination that numeric criteria are necessary in the State of California to protect human health and the environment. The Clean Water Act requires States to adopt numeric water quality criteria for priority toxic pollutants for which EPA has issued criteria guidance, the presence or discharge of which could reasonably be expected to interfere with maintaining designated uses.

EPA is promulgating this rule to fill a gap in California water quality standards that was created in 1994 when a State court overturned the State's water quality control plans which contained water quality criteria for priority toxic pollutants. Thus, the State of California has been without numeric water quality criteria for many priority toxic pollutants as required by the Clean Water Act, necessitating this action by EPA. These Federal criteria are legally applicable in the State of California for inland surface waters, enclosed bays and estuaries for all purposes and programs under the Clean Water Act.

EFFECTIVE DATE: This rule shall be effective May 18, 2000.

ADDRESSES: The administrative record for today's final rule is available for public inspection at the U.S. Environmental Protection Agency, Region 9, Water Division, 75 Hawthorne Street, San Francisco, California 94105, between the hours of 8:00 a.m. and 4:30 p.m. For access to the administrative record, call Diane E. Fleck, P.E., Esq. at 415 744–1984 for an appointment. A reasonable fee will be charged for photocopies.

FOR FURTHER INFORMATION CONTACT: Diane E. Fleck, P.E., Esq. or Philip Woods, U.S. Environmental Protection Agency, Region 9, Water Division, 75 Hawthorne Street, San Francisco, California 94105, 415–744–1984 or 415–744–1997, respectively.

SUPPLEMENTARY INFORMATION: This preamble is organized according to the following outline:

A. Potentially Affected Entities

Citizens concerned with water quality in California may be interested in this rulemaking. Entities discharging pollutants to waters of the United States in California could be affected by this rulemaking since water quality criteria are used by the State in developing National Pollutant Discharge Elimination System (NPDES) permit limits. Categories and entities that ultimately may be affected include:

Category	Examples of potentially affected entities
Industry	Industries discharging pollutants to surface waters in California or to publicly-owned treatment works.
Municipalities	Publicly-owned treatment works discharging pollutants to surface waters in California

This table is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. This table lists the types of entities that EPA is now aware could potentially be affected by this action. Other types of entities not listed in the table could also be affected. To determine whether your facility might be affected by this action, you should carefully examine the applicability criteria in § 131.38(c). If you have questions regarding the applicability of this action to a particular entity, consult the persons listed in the preceding **FOR FURTHER INFORMATION CONTACT** section.

B. Introduction and Overview

1. Introduction

This section introduces the topics which are addressed in the preamble and provides a brief overview of EPA's basis and rationale for promulgating Federal criteria for the State of California. Section C briefly describes the evolution of the efforts to control toxic pollutants; these efforts include the changes enacted in the 1987 CWA Amendments, which are the basis for this rule. Section D summarizes California's efforts since 1987 to implement the requirements of CWA section 303(c)(2)(B) and describes EPA's procedure and actions for determining whether California has fully implemented CWA section 303(c)(2)(B). Section E provides the rationale and approach for developing this final rule, including a discussion of EPA's legal basis for this final rule. Section F describes the development of the criteria included in this rule. Section G summarizes the provisions of the final rule and discusses implementation issues. Sections H, I, J, K , L, M, N, O, P, and Q briefly address the requirements of Executive Order 12866, the Unfunded Mandates Reform Act of 1995, the Regulatory Flexibility Act, the Paperwork Reduction Act, the Endangered Species Act, the Congressional Review Act, Executive Order 13084, Consultation and Coordination with Indian Tribal Governments, the National Technology Transfer and Advancement Act, and Executive Order 13132, Federalism, respectively.

The proposal for this rulemaking was published in the **Federal Register** on August 5, 1997. Changes from the proposal are generally addressed in the body of this preamble and specifically addressed in the response to comments document included in the administrative record for this rulemaking. EPA responded to all comments on the proposed rule, including comments received after the September 26, 1997, deadline. Although EPA is under no legal obligation to respond to late comments, EPA made a policy decision to respond to all comments.

Since detailed information concerning many of the topics in this preamble was published previously in the **Federal Register** in preambles for this and other rulemakings, references are frequently made to those preambles. Those rulemakings include: Water Quality Standards; Establishment of Numeric Criteria for Priority Toxic Pollutants for the State of California; Proposed Rule, 62 FR 42159, August 5, 1997 (referred to as the ''proposed CTR''); Water Quality Standards; Establishment of Numeric Criteria for Priority Toxic Pollutants, 57 FR 60848, December 22, 1992 (referred to as the ''National Toxics Rule'' or ''NTR''); and the NTR as amended by Administrative Stay of Federal Water Quality Criteria for Metals and Interim Final Rule, Water Quality Standards; Establishment of Numeric Criteria for Priority Toxic Pollutants; States' Compliance—Revision of Metals Criteria, 60 FR 22228, May 4, 1995 (referred to as the ''National Toxics Rule [NTR], as amended''). The NTR, as amended, is codified at 40 CFR 131.36. A copy of the proposed CTR and its preamble, and the NTR, as amended, and its preambles are contained in the administrative record for this rulemaking.

EPA is making this final rule effective upon publication. Under the Administrative Procedure Act, 5 U.S.C. 553(d)(3), agencies must generally publish a rule no more than 30 days prior to the effective date of the rule except as otherwise provided for by the Agency for good cause. The purpose of the 30-day waiting period is to give affected parties a reasonable time to adjust their behavior before the final rule takes effect. See *Omnipoint Corp.* v. *F.C.C.,* 78 F.3d 620, 630–631 (D.C. Cir. 1996); *Riverbend Farms, Inc.* v. *Madigan*, 958 F.2d 1479, 1485 (9th Cir. 1992).

In this instance, EPA finds good cause to make the final rule effective upon publication. In order to find good cause, an Agency needs to find that the 30-day period would be: (1) Impracticable, (2) unnecessary, or (3) contrary to the public interest. Here EPA is relying on the second reason to support its finding of good cause. EPA also notes that the State has requested EPA to make the rule immediately effective.

EPA finds that in this instance, waiting 30 days to make the rule effective is unnecessary. As explained in further detail elsewhere in this preamble, this rule is not self implementing; rather it establishes ambient conditions that the State of California will implement in future permit proceedings. These permit proceedings will, by regulation, take longer than 30 days to complete. This means that although the rule is immediately effective, no discharger's conduct would be altered under the rule in less than 30 days, and therefore the 30-day period is unnecessary.

2. Overview

This final rule establishes ambient water quality criteria for priority toxic pollutants in the State of California. The criteria in this final rule will supplement the water quality criteria promulgated for California in the NTR, as amended. In 1991, EPA approved a number of water quality criteria (discussed in section D), for the State of California. Since EPA had approved these criteria, it was not necessary to include them in the 1992 NTR for these criteria. However, the EPA-approved criteria were subsequently invalidated in State litigation. Thus, this final rule contains criteria to fill the gap created by the State litigation.

This final rule does not change or supersede any criteria previously promulgated for the State of California in the NTR, as amended. Criteria which EPA promulgated for California in the NTR, as amended, are footnoted in the final table at 131.38(b)(1), so that readers may see the criteria promulgated in the NTR, as amended, for California and the criteria promulgated through this rulemaking for California in the same table. This final rule is not intended to apply to waters within Indian Country. EPA recognizes that there are possibly waters located wholly or partly in Indian Country that are included in the State's basin plans. EPA will work with the State and Tribes to identify any such waters and determine whether further action to protect water quality in Indian Country is necessary.

This rule is important for several environmental, programmatic and legal reasons. Control of toxic pollutants in surface waters is necessary to achieve the CWA's goals and objectives. Many of California's monitored river miles, lake acres, and estuarine waters have elevated levels of toxic pollutants. Recent studies on California water bodies indicate that elevated levels of toxic pollutants exist in fish tissue which result in fishing advisories or bans. These toxic pollutants can be attributed to, among other sources, industrial and municipal discharges.

Water quality standards for toxic pollutants are important to State and EPA efforts to address water quality problems. Clearly established water quality goals enhance the effectiveness of many of the State's and EPA's water programs including permitting, coastal water quality improvement, fish tissue quality protection, nonpoint source controls, drinking water quality protection, and ecological protection. Numeric criteria for toxic pollutants allow the State and EPA to evaluate the adequacy of existing and potential control measures to protect aquatic ecosystems and human health. Numeric criteria also provide a more precise basis for deriving water quality-based effluent limitations (WQBELs) in

National Pollutant Discharge Elimination System (NPDES) permits and wasteload allocations for total maximum daily loads (TMDLs) to control toxic pollutant discharges. Congress recognized these issues when it enacted section 303(c)(2)(B) to the CWA.

While California recognizes the need for applicable water quality standards for toxic pollutants, its adoption efforts have been stymied by a variety of factors. The Administrator has decided to exercise her CWA authorities to move forward the toxic control program, consistent with the CWA and with the State of California's water quality standards program.

Today's action will also help restore equity among the States. The CWA is designed to ensure all waters are sufficiently clean to protect public health and/or the environment. The CWA allows some flexibility and differences among States in their adopted and approved water quality standards, but it should be implemented in a manner that ensures a level playing field among States. Although California has made important progress toward satisfying CWA requirements, it has not satisfied CWA section 303(c)(2)(B) by adopting numeric water quality criteria for toxic pollutants. This section was added to the CWA by Congress in 1987. Prior to today, the State of California had been the only State in the Nation for which CWA section 303(c)(2)(B) had remained substantially unimplemented after EPA's promulgation of the NTR in December of 1992. Section 303(c)(4) of the CWA authorizes the EPA Administrator to promulgate standards where necessary to meet the requirements of the Act. The Administrator determined that this rule was a necessary and important component for the implementation of CWA section 303(c)(2)(B) in California.

EPA acknowledges that the State of California is working to satisfy CWA section 303(c)(2)(B). When the State formally adopts, and EPA approves, criteria consistent with statutory requirements, as envisioned by Congress in the CWA, EPA intends to stay this rule. If within the applicable time frame for judicial review, the States' standards are challenged, EPA will withdraw this rule after such judicial review is complete and the State standards are sustained.

C. Statutory and Regulatory Background

The preamble to the August 5, 1997, proposed rule provided a general discussion of EPA's statutory and regulatory authority to promulgate water quality criteria for the State of California. See 62 FR 42160–42163. EPA is including that discussion in the record for the final rule. Commenters questioned EPA's authority to promulgate certain aspects of the proposal. EPA is responding to those comments in the appropriate sections of this preamble, and in the response to comments document included in the administrative record for this rulemaking. Where appropriate, EPA's responses expand upon the discussion of statutory and regulatory authority found in the proposal.

D. California Water Quality Standards Actions

1. California Regional Water Quality Control Board Basin Plans, and the Inland Surface Waters Plan (ISWP) and the Enclosed Bays and Estuaries Plan (EBEP) of April 1991

The State of California regulates water quality through its State Water Resources Control Board (SWRCB) and through nine Regional Water Quality Control Boards (RWQCBs). Each of the nine RWQCBs represents a different geographic area; area boundaries are generally along watershed boundaries. Each RWQCB maintains a Basin Plan which contains the designated uses of the water bodies within its respective geographic area within California. These designated uses (or ''beneficial uses'' under State law) together with legally-adopted criteria (or ''objectives'' under State law), comprise water quality standards for the water bodies within each of the Basin areas. Each of the nine RWQCBs undergoes a triennial basin planning review process, in compliance with CWA section 303. The SWRCB provides assistance to the RWQCBs.

Most of the Basin Plans contain conventional pollutant objectives such as dissolved oxygen. None of the Basin Plans contains a comprehensive list of priority toxic pollutant criteria to satisfy CWA section 303(c)(2)(B). The nine RWQCBs and the SWRCB had intended that the priority toxic pollutant criteria contained in the three SWRCB statewide plans, the Inland Surface Waters Plan (ISWP), the Enclosed Bays and Estuaries Plan (EBEP), and the Ocean Plan, apply to all basins and satisfy CWA section 303(c)(2)(B).

On April 11, 1991, the SWRCB adopted two statewide water quality control plans, the ISWP and the EBEP. These statewide plans contained narrative and numeric water quality criteria for toxic pollutants, in part to satisfy CWA section 303(c)(2)(B). The water quality criteria contained in the SWRCB statewide plans, together with the designated uses in each of the Basin Plans, created a set of water quality standards for waters within the State of California.

Specifically, the two plans established water quality criteria or objectives for all fresh waters, bays and estuaries in the State. The plans contained water quality criteria for some priority toxic pollutants, provisions relating to whole effluent toxicity, implementation procedures for point and nonpoint sources, and authorizing compliance schedule provisions. The plans also included special provisions affecting waters dominated by reclaimed water (labeled as Category (a) waters), and waters dominated by agricultural drainage and constructed agricultural drains (labeled as Category (b) and (c) waters, respectively).

2. EPA's Review of California Water Quality Standards for Priority Toxic Pollutants in the ISWP and EBEP, and the National Toxics Rule

The EPA Administrator has delegated the responsibility and authority for review and approval or disapproval of all new or revised State water quality standards to the EPA Regional Administrators (see 40 CFR 131.21). Thus, State actions under CWA section 303(c)(2)(B) are submitted to the appropriate EPA Regional Administrator for review and approval.

In mid-April 1991, the SWRCB submitted to EPA for review and approval the two statewide water quality control plans, the ISWP and the EBEP. On November 6, 1991, EPA Region 9 formally concluded its review of the SWRCB's plans. EPA approved the narrative water quality criterion and the toxicity criterion in each of the plans. EPA also approved the numeric water quality criteria contained in both plans, finding them to be consistent with the requirements of section 303(c)(2)(B) of the CWA and with EPA's national criteria guidance published pursuant to section 304(a) of the CWA.

EPA noted the lack of criteria for some pollutants, and found that, because of the omissions, the plans did not fully satisfy CWA section 303(c)(2)(B). The plans did not contain criteria for all listed pollutants for which EPA had published national criteria guidance. The ISWP contained human health criteria for only 65 pollutants, and the EBEP contained human health criteria for only 61 pollutants for which EPA had issued section 304(a) guidance criteria. Both the ISWP and EBEP contained aquatic life criteria for all pollutants except cyanide and chromium III (freshwater only) for which EPA has CWA section

304(a) criteria guidance. The SWRCB's administrative record stated that all priority pollutants with EPA criteria guidance were likely to be present in California waters. However, the SWRCB's record contained insufficient information to support a finding that the excluded pollutants were not reasonably expected to interfere with designated uses of the waters of the State.

Although EPA approved the statewide selenium objective in the ISWP and EBEP, EPA disapproved the objective for the San Francisco Bay and Delta, because there was clear evidence that the objective would not protect the designated fish and wildlife uses (the California Department of Health Services had issued waterfowl consumption advisories due to selenium concentrations, and scientific studies had documented selenium toxicity to fish and wildlife). EPA restated its commitment to object to National Pollutant Discharge Elimination System (NPDES) permits issued for San Francisco Bay that contained effluent limits based on an objective greater than 5 parts per billion (ppb) (four day average) and 20 ppb (1 hour average), the freshwater criteria. EPA reaffirmed its disapproval of Californias' site-specific selenium objective for portions of the San Joaquin River, Salt Slough, and Mud Slough. EPA also disapproved of the categorical deferrals and exemptions. These disapprovals included the disapproval of the State's deferral of water quality objectives to effluent dominated streams (Category a) and to streams dominated by agricultural drainage (Category b), and the disapproval of the exemption of water quality objectives to constructed agricultural drains (Category c). EPA found the definitions of the categories imprecise and overly broad which could have led to an incorrect interpretation.

Since EPA had disapproved portions of each of the California statewide plans which were necessary to satisfy CWA section 303(c)(2)(B), certain disapproved aspects of California's water quality standards were included in EPA's promulgation of the National Toxics Rule (NTR) (40 CFR 131.36, 57 FR 60848). EPA promulgated specific criteria for certain water bodies in California.

The NTR was amended, effective April 14, 1995, to stay certain metals criteria which had been promulgated as total recoverable. Effective April 15, 1995, EPA promulgated interim final metals criteria as dissolved concentrations for those metals which had been stayed (Administrative Stay of Federal Water Quality Criteria for Metals and Interim Final Rule, Water Quality Standards; Establishment of Numeric Criteria for Priority Toxic Pollutants; States' Compliance—Revision of Metals Criteria; 60 FR 22228, 22229, May 4, 1995 [the NTR, as amended]). The stay was in response to a lawsuit against EPA challenging, among other issues, metals criteria expressed as total recoverable concentrations. A partial Settlement Agreement required EPA to stay specific metals criteria in the NTR. EPA then promulgated certain metals criteria in the dissolved form through the use of conversion factors. These factors are listed in the NTR, as amended. A scientific discussion of these criteria is found in a subsequent section of this preamble.

Since certain criteria have already been promulgated for specific water bodies in the State of California in the NTR, as amended, they are not within the scope of today's final rule. However, for clarity in reading a comprehensive rule for the State of California, these criteria are incorporated into 40 CFR 131.38(d)(2). Footnotes to the Table in 40 CFR 131.38(b)(1) and 40 CFR 131.38(d)(3) clarify which criteria (and for which specific water bodies) were promulgated by the NTR, as amended, and are therefore excluded from this final rule. The appropriate (freshwater or saltwater) aquatic life criteria which were promulgated in the NTR, as amended, for all inland surface waters and enclosed bays and estuaries include: chromium III and cyanide. The appropriate (water and organism or organism only) human health criteria which were promulgated in the NTR, as amended, for all inland surface waters and enclosed bays and estuaries include:

antimony
thallium
asbestos
acrolein
acrylonitrile
carbon tetrachloride
chlorobenzene
1,2-dichloroethane
1,1-dichloroethylene
1,3-dichloropropylene
ethylbenzene
1,1,2,2-tetrachloroethane
tetrachloroethylene
1,1,2-trichloroethane
trichloroethylene
vinyl chloride
2,4-dichlorophenol
2-methyl-4,6-dinitrophenol
2,4-dinitrophenol
benzidine
bis(2-chloroethyl)ether
bis(2-ethylhexyl)phthalate
3,3-dichlorobenzidine
diethyl phthalate
dimethyl phthalate
di-n-butyl phthalate
2,4-dinitrotoluene
1,2-diphenylhydrazine
hexachlorobutadiene
hexachlorocyclopentadiene
hexachloroethane
isophorone
nitrobenzene
n-nitrosodimethylamine
n-nitrosodiphenylamine

Other pollutant criteria were promulgated in the NTR, as amended, for specific water bodies, but not all inland surface waters and enclosed bays and estuaries.

3. Status of Implementation of CWA Section 303(c)(2)(B)

Shortly after the SWRCB adopted the ISWP and EBEP, several dischargers filed suit against the State alleging that it had not adopted the two plans in compliance with State law. The plaintiffs in a consolidated case included: the County of Sacramento, Sacramento County Water Agency; Sacramento Regional County Sanitation District; the City of Sacramento; the City of Sunnyvale; the City of San Jose; the City of Stockton; and Simpson Paper Company.

The dischargers alleged that the State had not adopted the ISWP and EBEP in compliance with the California Administrative Procedures Act (Gov Code. Section 11340, *et seq.*), the California Environmental Quality Act (Pub. Re Code, Section 21000, *et seq.*), and the Porter-Cologne Act (Wat. Code, Section 13200, *et seq.*). The allegation that the State did not sufficiently consider economics when adopting water quality objectives, as allegedly required by Section 13241 of the Porter Cologne Act, was an important issue in the litigation.

In October of 1993, the Superior Court of California, County of Sacramento, issued a tentative decision in favor of the dischargers. In March of 1994, the Court issued a substantively similar final decision in favor of the dischargers. Final judgments from the Court in July of 1994 ordered the SWRCB to rescind the ISWP and EBEP. On September 22, 1994, the SWRCB formally rescinded the two statewide water quality control plans. The State is currently in the process of readopting water quality control plans for inland surface waters, enclosed bays and estuaries.

CWA section 303(c)(2)(B) was fully implemented in the State of California from December of 1992, when the NTR was promulgated, until September of 1994, when the SWRCB was required to rescind the ISWP and EBEP. The provisions for California in EPA's NTR together with the approved portions of

California's ISWP and EBEP implemented the requirements of CWA section 303(c)(2)(B). However, since September of 1994, when the SWRCB rescinded the ISWP and EBEP, the requirements of section 303(c)(2)(B) have not been fully implemented in California.

The scope of today's rule is to re-establish criteria for the remaining priority toxic pollutants to meet the requirements of section 303(c)(2)(B) of the CWA. Pursuant to section 303(c)(4), the Administrator has determined that it is necessary to include in today's action criteria for priority toxic pollutants, which are not covered by the NTR, as amended, or by the State through EPA-approved site-specific criteria, for waters of the United States in the State of California.

4. State-Adopted, Site-Specific Criteria for Priority Toxic Pollutants

The State has the discretion to develop site-specific criteria when appropriate e.g., when statewide criteria appear over-or under-protective of designated uses. Periodically, the State through its RWQCBs will adopt site-specific criteria for priority toxic pollutants within respective Basin Plans. These criteria are intended to be effective throughout the Basin or throughout a designated water body. Under California law, these criteria must be publicly reviewed and approved by the RWQCB, the SWRCB, and the State's Office of Administrative Law (OAL). Once this adoption process is complete, the criteria become State law.

These criteria must be submitted to the EPA Regional Administrator for review and approval under CWA section 303. These criteria are usually submitted to EPA as part of a RWQCB Basin Plan Amendment, after the Amendment has been adopted under the State's process and has become State law.

a. State-Adopted Site-Specific Criteria Under EPA Review

The State of California has recently reviewed and updated all of its RWQCB Basin Plans. All of the Basin Plans have completed the State review and adoption process and have been submitted to EPA for review and approval. Some of the Basin Plans contain site-specific criteria. In these cases, the State-adopted site-specific criteria are used for water quality programs.

EPA has not yet concluded consultation under the Endangered Species Act with the U.S. Department of Interior, Fish and Wildlife Service, and the U.S. Department of Commerce, National Marine Fisheries Service, on EPA's tentative approval/disapproval actions on the RWQCB Basin Plans. In this situation, the more stringent of the two criteria (the State-adopted site-specific criteria in the RWQCB Basin Plans, or the Federal criteria in this final rule), would be used for water quality programs including the calculation of water quality-based effluent criteria in National Pollutant Discharge Elimination System (NPDES) permits.

b. State-Adopted Site-Specific Criteria With EPA Approval

In several cases, the EPA Regional Administrator has already reviewed and approved State-adopted site-specific criteria within the State of California. Several of these cases are discussed in this section. All of the EPA approval letters referenced in today's preamble are contained in the administrative record for today's rule.

Sacramento River: EPA has approved site-specific acute criteria for copper, cadmium and zinc in the Sacramento River, upstream of Hamilton City, in the Central Valley Region (RWQCB for the Central Valley Region) of the State of California. EPA approved these site-specific criteria by letter dated August 7, 1985. Specifically, EPA approved for the Sacramento River (and tributaries) above Hamilton City, a copper criterion of 5.6 µg/l (maximum), a zinc criterion of 16 µg/l (maximum) and a cadmium criterion of 0.22 µg/l (maximum), all in the dissolved form using a hardness of 40 mg/l as CaCO3. (These criteria were actually adopted by the State and approved by EPA as equations which vary with hardness.) These ''maximum'' criteria correspond to acute criteria in today's final rule. Therefore, Federal acute criteria for copper, cadmium, and zinc for the Sacramento River (and tributaries) above Hamilton City are not necessary to protect the designated uses and are not included in the final rule. However, the EPA Administrator is making a finding that it is necessary to include chronic criteria for copper, cadmium and zinc for the Sacramento River (and tributaries) above Hamilton City, as part of the statewide criteria promulgated in today's final rule.

San Joaquin River: The selenium criteria in this rule are not applicable to portions of the San Joaquin River, in the Central Valley Region, because selenium criteria have been either previously approved by EPA or previously promulgated by EPA as part of the NTR. EPA approved and disapproved State-adopted site-specific selenium criteria in portions of the San Joaquin River, in the Central Valley Region of the State of California (RWQCB for the Central Valley Region). EPA's determination on these site-specific criteria is contained in a letter dated April 13, 1990.

Specifically, EPA approved for the San Joaquin River, mouth of Merced River to Vernalis, an aquatic life selenium criterion of 12 µg/l (maximum with the understanding that the instantaneous maximum concentration may not exceed the objective more than once every three years). Today's final rule does not affect this Federally-approved, State-adopted site-specific acute criterion, and it remains in effect for the San Joaquin River, mouth of Merced River to Vernalis. Therefore, an acute criterion for selenium in the San Joaquin River, mouth of Merced River to Vernalis is not necessary to protect the designated use and thus is not included in this final rule.

By letter dated April 13, 1990, EPA also approved for the San Joaquin River, mouth of Merced River to Vernalis, a State-adopted site-specific aquatic life selenium criterion of 5 µg/l (monthly mean); however, EPA disapproved a State-adopted site-specific selenium criterion of 8 µg/l (monthly mean—critical year only) for these waters. Subsequently, EPA promulgated a chronic selenium criterion of 5 µg/l (4 day average) for waters of the San Joaquin River from the mouth of the Merced River to Vernalis in the NTR. This chronic criterion applies to all water quality programs concerning the San Joaquin River, mouth of Merced River to Vernalis. Today's final rule does not affect the Federally-promulgated chronic selenium criterion of 5 µg/l (4 day average) set forth in the NTR. This previously Federally-promulgated criterion remains in effect for the San Joaquin River, mouth of Merced River to Vernalis.

Grassland Water District, San Luis National Wildlife Refuge, and Los Banos State Wildlife Refuge: EPA approved for the Grassland Water District, San Luis National Wildlife Refuge, and Los Banos State Wildlife Refuge, a State-adopted site-specific aquatic life selenium criterion of 2 µg/l (monthly mean) by letter dated April 13, 1990. This Federally-approved, State-adopted site-specific chronic criterion remains in effect for the Grassland Water District, San Luis National Wildlife Refuge and Los Banos State Wildlife Refuge. Therefore it is not necessary to include in today's final rule, a chronic criterion for selenium for the Grassland Water District, San Luis National Wildlife Refuge and Los Banos State Wildlife Refuge, and thus, it is not included in this final rule.

San Francisco Regional Board Basin Plan of 1986: EPA approved several priority toxic pollutant objectives (CWA criteria) that were contained in the1986 San Francisco Regional Board Basin Plan, as amended by SWRCB Resolution Numbers 87–49, 87–82 and 87–92, by letters dated September 2, 1987 and December 24, 1987. This Basin Plan, the SWRCB Resolutions, and the EPA approval letters are contained in the administrative record for this rulemaking. It is not necessary to include these criteria for priority toxic pollutants that are contained in the San Francisco Regional Board's 1986 Basin Plan as amended, and approved by EPA. Priority pollutants in this situation are footnoted in the matrix at 131.38(b)(1) with footnote ''b.'' Where gaps exist in the State adoption and EPA approval of priority toxic pollutant objectives, the criteria in today's rule apply.

EPA is assigning ''human health, water and organism consumption'' criteria to waters with the States' municipal or ''MUN'' beneficial use designation in the Basin Plan. Also, some pollutants regulated through the Basin Plan have different averaging periods, *e.g.,* one hour as compared with the rule's ''short-term.'' However, where classes of chemicals, such as polynuclear aromatic hydrocarbons, or PAHs, and phenols, are regulated through the Basin Plan, but not specific chemicals within the category, specific chemicals within the category are regulated by today's rule.

E. Rationale and Approach for Developing the Final Rule

This section explains EPA's legal basis for today's final rule, and discusses EPA's general approach for developing the specific requirements for the State of California.

1. Legal Basis

CWA section 303(c) specifies that adoption of water quality standards is primarily the responsibility of the States. However, CWA section 303(c) also describes a role for the Federal government to oversee State actions to ensure compliance with CWA requirements. If EPA's review of the States' standards finds flaws or omissions, then the CWA authorizes EPA to correct the deficiencies (see CWA section 303(c)(4)). This water quality standards promulgation authority has been used by EPA to issue final rules on several separate occasions, including the NTR, as amended, which promulgated criteria similar to those included here for a number of States. These actions have addressed both insufficiently protective State criteria and/or designated uses and failure to adopt needed criteria. Thus, today's action is not unique.

The CWA in section 303(c)(4) provides two bases for promulgation of Federal water quality standards. The first basis, in paragraph (A), applies when a State submits new or revised standards that EPA determines are not consistent with the applicable requirements of the CWA. If, after EPA's disapproval, the State does not amend its rules so as to be consistent with the CWA, EPA is to promptly propose appropriate Federal water quality standards for that State. The second basis for an EPA action is in paragraph (B), which provides that EPA shall promptly initiate promulgation ''* * * in any case where the Administrator determines that a revised or new standard is necessary to meet the requirements of this Act.'' EPA is using section 303(c)(4)(B) as the legal basis for today's final rule.

As discussed in the preamble to the NTR, the Administrator's determination under CWA section 303(c)(4) that criteria are necessary to meet the requirements of the Act could be supported in several ways. Consistent with EPA's approach in the NTR, EPA interprets section 303(c)(2)(B) of the CWA to allow EPA to act where the State has not succeeded in establishing numeric water quality standards for toxic pollutants. This inaction can be the basis for the Administrator's determination under section 303(c)(4) that new or revised criteria are necessary to ensure designated uses are protected.

EPA does not believe that it is necessary to support the criteria in today's rule on a pollutant-specific, water body-by-water-body basis. For EPA to undertake an effort to conduct research and studies of each stream segment or water body across the State of California to demonstrate that for each toxic pollutant for which EPA has issued CWA section 304(a) criteria guidance there is a ''discharge or presence'' of that pollutant which could reasonably ''be expected to interfere with'' the designated use would impose an enormous administrative burden and would be contrary to the statutory directive for swift action manifested by the 1987 addition of section 303(c)(2)(B) to the CWA. Moreover, because these criteria are ambient criteria that define attainment of the designated uses, their application to all water bodies will result in additional controls on dischargers only where necessary to protect the designated uses.

EPA's interpretation of section 303(c)(2)(B) is supported by the language of the provision, the statutory framework and purpose of section 303, and the legislative history. In adding section 303(c)(2)(B) to the CWA, Congress understood the existing requirements in section 303(c)(1) for States to conduct triennial reviews of their water quality standards and submit the results of those reviews to EPA and in section 303(c)(4)(B) for promulgation. CWA section 303(c) includes numerous deadlines and section 303(c)(4) directs the Administrator to act ''promptly'' where the Administrator determines that a revised or new standard is necessary to meet the requirements of the Act. Congress, by linking section 303(c)(2)(B) to the section 303(c)(1) three-year review period, gave States a last chance to correct this deficiency on their own. The legislative history of the provision demonstrates that chief Senate sponsors, including Senators Stafford, Chaffee and others wanted the provision to eliminate State and EPA delays and force quick action. Thus, to interpret CWA section 303(c)(2)(B) and (c)(4) to require such a cumbersome pollutant specific effort on each stream segment would essentially render section 303(c)(2)(B) meaningless. The provision and its legislative background indicate that the Administrator's determination to invoke section 303(c)(4)(B) authority can be met by the Administrator making a generic finding of inaction by the State without the need to develop pollutant specific data for individual stream segments. Finally, the reference in section 303(c)(2)(B) to section 304(a) criteria suggests that section 304(a) criteria serve as default criteria; that once EPA has issued them, States were to adopt numeric criteria for those pollutants based on the 304(a) criteria, unless they had other scientifically defensible criteria. EPA also notes that this rule follows the approach EPA took nationally in promulgating the NTR for States that failed to comply with CWA section 303(c)(2)(B). 57 FR 60848, December 22, 1992. EPA incorporates the discussion in the NTR preamble as part of this rulemaking record.

This determination is supported by information in the rulemaking record showing the discharge or presence of priority toxic pollutants throughout the State. While this data is not necessarily complete, it constitutes a strong record supporting the need for numeric criteria for priority toxic pollutants with section 304(a) criteria guidance where the State does not have numeric criteria.

Today's final rule would not impose any undue or inappropriate burden on the State of California or its dischargers. It merely puts in place numeric criteria

for toxic pollutants that are already used in other States in implementing CWA programs. Under this rulemaking, the State of California retains the ability to adopt alternative water quality criteria simply by completing its criteria adoption process. Upon EPA approval of those criteria, EPA will initiate action to stay the Federally-promulgated criteria and subsequently withdraw them.

2. Approach for Developing This Rule

In summary, EPA developed the criteria promulgated in today's final rule as follows. Where EPA promulgated criteria for California in the NTR, EPA has not acted to amend the criteria in the NTR. Where criteria for California were not included in the NTR, EPA used section 304(a) National criteria guidance documents as a starting point for the criteria promulgated in this rule. EPA then determined whether new information since the development of the national criteria guidance documents warranted any changes. New information came primarily from two sources. For human health criteria, new or revised risk reference doses and cancer potency factors on EPA's Integrated Risk Information System (IRIS) as of October 1996 form the basis for criteria values (see also 63 FR 68354). For aquatic life criteria, updated data sets resulting in revised criteria maximum concentrations (CMCs) and criteria continuous concentrations (CCCs) formed the basis for differences from the national criteria guidance documents. Both of these types of changes are discussed in more detail in the following sections. This revised information was used to develop the water quality criteria promulgated here for the State of California.

F. Derivation of Criteria

1. Section 304(a) Criteria Guidance Process

Under CWA section 304(a), EPA has developed methodologies and specific criteria guidance to protect aquatic life and human health. These methodologies are intended to provide protection for all surface waters on a national basis. The methodologies have been subject to public review, as have the individual criteria guidance documents. Additionally, the methodologies have been reviewed by EPA's Science Advisory Board (SAB) of external experts.

EPA has included in the record of this rule the aquatic life methodology as described in ''Appendix B—Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses'' to the ''Water Quality Criteria Documents; Availability'' (45 FR 79341, November 28, 1980) as amended by the ''Summary of Revisions to Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses'' (50 FR 30792, July 29, 1985). (**Note:** Throughout the remainder of this preamble, this reference is described as the 1985 Guidelines. Any page number references are to the actual guidance document, not the notice of availability in the **Federal Register**. A copy of the 1985 Guidelines is available through the National Technical Information Service (PB85–227049), is in the administrative record for this rule, and is abstracted in Appendix A of *Quality Criteria for Water,* 1986.) EPA has also included in the administrative record of this rule the human health methodology as described in ''Appendix C—Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents'' (45 FR 79347, November 28, 1980). (Note: Throughout the remainder of this preamble, this reference is described as the Human Health Guidelines or the 1980 Guidelines.) EPA also recommends that the following be reviewed: ''Appendix D—Response to Comments on Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses,'' (45 FR 79357, November 28, 1980); ''Appendix E—Responses to Public Comments on the Human Health Effects Methodology for Deriving Ambient Water Quality Criteria'' (45 FR 79368, November 28, 1980); and ''Appendix B—Response to Comments on Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses'' (50 FR 30793, July 29, 1985). EPA placed into the administrative record for this rulemaking the most current individual criteria guidance for the priority toxic pollutants included in today's rule. (**Note:** All references to appendices are to the associated **Federal Register** publication.)

EPA received many comments related to the issue of what criteria should apply in the CTR if the CWA section 304(a) criteria guidance is undergoing re-evaluation, or if new data are developed that may affect a recommended criterion. As science is always evolving, EPA is faced with the challenge of promulgating criteria that reflect the best science and sound science. EPA addressed this challenge in some detail in its **Federal Register** notice that contained the Agency's current section 304(a) criteria guidance (63 FR 68335, December 10, 1998). There, EPA articulated its policy, reiterated here, that the existing criteria guidance represent the Agency's best assessment until such time as EPA's re-evaluation of a criteria guidance value for a particular chemical is complete. The reason for this is that both EPA's human health criteria guidance and aquatic life criteria guidance are developed taking into account numerous variables. For example, for human health criteria guidance, EPA evaluates many diverse toxicity studies, whose results feed into a reference dose or cancer potency estimate that, along with a number of exposure factors and determination of risk level, results in a guidance criterion. For aquatic life, EPA evaluates many diverse aquatic toxicity studies to determine chronic and acute toxicity taking into account how other factors (such as pH, temperature or hardness) affect toxicity. EPA also, to the extent possible, addresses bioaccumulation or bioconcentration. EPA then uses this toxicity information along with exposure information to determine the guidance criterion. Importantly, EPA subjects such evaluation to peer review and/or public comment.

For these reasons, EPA generally does not make a change to the 304(a) criteria guidance based on a partial picture of the evolving science. This makes sense, because to address one piece of new data without looking at all relevant data is less efficient and results in regulatory impacts that may go back and forth, when in the end, the criteria guidance value does not change that much. Certain new changes, however, do warrant change in criteria guidance, such as a change in a value in EPA's Integrated Risk Information System (IRIS) because it represents the Agency consensus about human health impacts. These changes are sufficiently examined across the Agency such that EPA believes they can be incorporated into EPA's water quality criteria guidance. EPA has followed this approach in the CTR. Included in the administrative record for today's rule is a document entitled ''Status of Clean Water Act Section 304(a) Criteria'' which further explains EPA's policy on managing change to criteria guidance.

2. Aquatic Life Criteria

Aquatic life criteria may be expressed in numeric or narrative form. EPA's 1985 Guidelines describe an objective, internally consistent and appropriate way of deriving chemical-specific, numeric water quality criteria for the protection of the presence of, as well as

the uses of, both fresh and salt water aquatic organisms.

An aquatic life criterion derived using EPA's CWA section 304(a) method ''might be thought of as an estimate of the highest concentration of a substance in water which does not present a significant risk to the aquatic organisms in the water and their uses.'' (45 FR 79341.) EPA's guidelines are designed to derive criteria that protect aquatic communities. EPA's 1985 Guidelines attempt to provide a reasonable and adequate amount of protection with only a small possibility of substantial overprotection or underprotection. As discussed in detail below, there are several individual factors which may make the criteria somewhat overprotective or underprotective. The approach EPA is using is believed to be as well balanced as possible, given the state of the science.

Numerical aquatic life criteria derived using EPA's 1985 Guidelines are expressed as short-term and long-term averages, rather than one number, in order that the criterion more accurately reflect toxicological and practical realities. The combination of a criterion maximum concentration (CMC), a short-term concentration limit, and a criterion continuous concentration (CCC), a four-day average concentration limit, are designed to provide protection of aquatic life and its uses from acute and chronic toxicity to animals and plants, without being as restrictive as a one-number criterion would have to be (1985 Guidelines, pages 4 & 5). The terms CMC and CCC are the formal names for the two (acute and chronic) values of a criterion for a pollutant; however, this document will also use the informal synonyms acute criterion and chronic criterion.

The two-number criteria are intended to identify average pollutant concentrations which will produce water quality generally suited to maintenance of aquatic life and designated uses while restricting the duration of excursions over the average so that total exposures will not cause unacceptable adverse effects. Merely specifying an average value over a time period may be insufficient unless the time period is short, because excursions higher than the average may kill or cause substantial damage in short periods.

A minimum data set of eight specified families is recommended for criteria development (details are given in the 1985 Guidelines, page 22). The eight specific families are intended to be representative of a wide spectrum of aquatic life. For this reason it is not necessary that the specific organisms tested be actually present in the water body. EPA's application of its guidelines to develop the criteria matrix in this rule is judged by the Agency to be appropriate for all waters of the United States (U.S.), and to all ecosystems (1985 Guidelines, page 4) including those waters of the U.S. and ecosystems in the State of California.

Fresh water and salt water (including both estuarine and marine waters) have different chemical compositions, and freshwater and saltwater species often do not inhabit the same water. To provide additional accuracy, criteria are developed for fresh water and for salt water.

For this rule, EPA updated freshwater aquatic life criteria contained in CWA section 304(a) criteria guidance first published in the early 1980's and later modified in the NTR, as amended, for the following ten pollutants: arsenic, cadmium, chromium (VI), copper, dieldrin, endrin, lindane (gamma BHC), nickel, pentachlorophenol, and zinc. The updates used as the basis for this rule are explained in a technical support document entitled, *1995 Updates: Water Quality Criteria Documents for the Protection of Aquatic Life in Ambient Water* (U.S. EPA–820–B–96–001, September 1996), available in the administrative record to this rulemaking; this document presents the derivation of each of the final CMCs and CCCs and the toxicity studies from which the updated freshwater criteria for the ten pollutants were derived.

The polychlorinated biphenyls (PCB) criteria in the criteria matrix for this rule differs from that in the NTR, as amended; for this rule, the criteria are expressed as the sum of seven aroclors, while for the NTR, as amended, the criteria are expressed for each of seven aroclors. The aquatic life criteria for PCBs in the CTR are based on the criteria contained in the 1980 criteria guidance document for PCBs which is included in the administrative record for this rule. This criteria document explains the derivation of aquatic life criteria based on total PCBs. For more information see the Response to Comments document for this rule. Today's chronic aquatic life criteria for PCBs are based on a final residue value (FRV). In EPA's guidelines for deriving aquatic life criteria, an FRV-based criterion is intended to prevent concentrations of pollutants in commercially or recreationally important aquatic species from affecting the marketability of those species or affecting the wildlife that consume aquatic life.

The proposed CTR included an updated freshwater and saltwater aquatic life criteria for mercury. In today's final rule, EPA has reserved the mercury criteria for freshwater and saltwater aquatic life, but is promulgating human health criteria for mercury for all surface waters in California. In some instances, the human health mercury criteria included in today's final rule may not protect some aquatic species or threatened or endangered species. In such instances, more stringent mercury limits may be determined and implemented through use of the State's narrative criterion. The reasons for reserving the mercury aquatic life numbers are explained in further detail in Section L, Endangered Species Act.

a. Freshwater Acute Selenium Criterion

EPA proposed a different freshwater acute aquatic life criterion for selenium for this rule than was promulgated in the NTR, as amended. EPA's proposed action was consistent with EPA's proposed selenium criterion maximum concentration for the Water Quality Guidance for the Great Lakes System (61 FR 58444, November 14, 1996). This proposal took into account data showing that selenium's two most prevalent oxidation states, selenite and selenate, present differing potentials for aquatic toxicity, as well as new data which indicated that various forms of selenium are additive. Additivity increases the toxicity of mixtures of different forms of the pollutant. The proposed approach produces a different selenium acute criterion concentration, or CMC, depending upon the relative proportions of selenite, selenate, and other forms of selenium that are present.

The preamble to the August 5, 1997, proposed rule provided a lengthy discussion of this proposed criterion for the State of California. See 62 FR 42160–42208. EPA incorporates that discussion here as part of this rulemaking record. In 1996, a similar discussion was included in the proposed rule for the Great Lakes System. Commenters questioned several aspects of the Great Lakes proposal. EPA is continuing to respond to those comments, and to follow up with additional literature review and toxicity testing. In addition, the U.S. FWS and U.S. NMFS (collectively, the Services) are concerned that EPA's proposed criterion may not be sufficiently protective of certain threatened and endangered species in California. Because the Services believe there is a lack of data to show for certain that the proposed criterion would not affect threatened and endangered species, the Services prefer that EPA further investigate the protectiveness of the

criterion before finalizing the proposed criterion. Therefore, EPA is not promulgating a final acute freshwater selenium criterion at this time.

b. Dissolved Metals Criteria

In December of 1992, in the NTR, EPA promulgated water quality criteria for several States that had failed to meet the requirements of CWA section 303(c)(2)(B). Included among the water quality criteria promulgated were numeric criteria for the protection of aquatic life for 11 metals: arsenic, cadmium, chromium (III), chromium (VI), copper, lead, mercury, nickel, selenium, silver and zinc. Criteria for two metals applied to the State of California: chromium III and selenium.

The Agency received extensive public comment during the development of the NTR regarding the most appropriate approach for expressing the aquatic life metals criteria. The principal issue was the correlation between metals that are measured and metals that are bioavailable and toxic to aquatic life. It is now the Agency's policy that the use of dissolved metal to set and measure compliance with aquatic life water quality standards is the recommended approach, because dissolved metal more closely approximates the bioavailable fraction of the metal in the water column than does total recoverable metal.

Since EPA's previous aquatic life criteria guidance had been expressed as total recoverable metal, to express the criteria as dissolved, conversion factors were developed to account for the possible presence of particulate metal in the laboratory toxicity tests used to develop the total recoverable criteria. EPA included a set of recommended freshwater conversion factors with its Metals Policy (see Office of Water Policy and Technical Guidance on Interpretation and Implementation of Aquatic Life Metals Criteria, Martha G. Prothro, Acting Assistant Administrator for Water, October 1, 1993). Based on additional laboratory evaluations that simulated the original toxicity tests, EPA refined the procedures used to develop freshwater conversion factors for aquatic life criteria. These new conversion factors were made available for public review and comment in the amendments to the NTR on May 4, 1995, at 60 FR 22229. They are also contained in today's rule at 40 CFR 131.38(b)(2).

The preamble to the August 5, 1997, proposed rule provided a more detailed discussion of EPA's metals policy concerning the aquatic life water quality criteria for the State of California. See 62 FR 42160–42208. EPA incorporates that discussion here as part of this rulemaking record. Many commenters strongly supported the Agency's policy on dissolved metals aquatic life criteria. A few commenters expressed an opinion that the metals policy may not provide criteria that are adequately protective of aquatic or other species. Responses to those comments are contained in a memo to the CTR record entitled ''Discussion of the Use of Dissolved Metals in the CTR'' (February 1, 2000, Jeanette Wiltse) and EPA's response to comments document which are both contained in the administrative record for the final rule.

Calculation of Aquatic Life Dissolved Metals Criteria: Metals criteria values for aquatic life in today's rule in the matrix at 131.38(b)(1) are shown as dissolved metal. These criteria have been calculated in one of two ways. For freshwater metals criteria that are hardness-dependent, the metals criteria value is calculated separately for each hardness using the table at 40 CFR 131.38(b)(2). (The hardness-dependent freshwater values presented in the matrix at 40 CFR 131.38(b)(1) have been calculated using a hardness of 100 mg/l as CaCO3 for illustrative purposes only.) The hardness-dependent criteria are then multiplied by the appropriate conversion factors in the table at 40 CFR 131.38(b)(2). Saltwater and freshwater metals criteria that are not hardness-dependent are calculated by taking the total recoverable criteria values (from EPA's national section 304(a) criteria guidance, as updated and described in section F.2.a.) before rounding, and multiplying them by the appropriate conversion factors. The final dissolved metals criteria values, as they appear in the matrix at 40 CFR 131.38(b)(1), are rounded to two significant figures.

Translators for Dissolved to Total Recoverable Metals Limits: EPA's National Pollutant Discharge Elimination System (NPDES) regulations require that limits for metals in permits be stated as total recoverable in most cases (see 40 CFR 122.45(c)) except when an effluent guideline specifies the limitation in another form of the metal, the approved analytical methods measure only dissolved metal, or the permit writer expresses a metal's limit in another form (*e.g.,* dissolved, specific valence, or total) when required to carry out provisions of the CWA. This is because the chemical conditions in ambient waters frequently differ substantially from those in the effluent and these differences result in changes in the partitioning between dissolved and absorbed forms of the metal. This means that if effluent limits were expressed in the dissolved form, additional particulate metal could dissolve in the receiving water causing the criteria to be exceeded. Expressing criteria as dissolved metal requires translation between different metal forms in the calculation of the permit limit so that a total recoverable permit limit can be established that will achieve water quality standards. Thus, it is important that permitting authorities and other authorities have the ability to translate between dissolved metal in ambient waters and total recoverable metal in effluent.

EPA has completed guidance on the use of translators to convert from dissolved metals criteria to total recoverable permit limits. The document, *The Metals Translator: Guidance for Calculating a Total Recoverable Permit Limit From a Dissolved Criterion* (EPA 823–B–96–007, June 1996), is included in the administrative record for today's rule. This technical guidance examines how to develop a metals translator which is defined as the fraction of total recoverable metal in the downstream water that is dissolved, *i.e.,* the dissolved metal concentration divided by the total recoverable metal concentration. A translator may take one of three forms: (1) It may be assumed to be equivalent to the criteria guidance conversion factors; (2) it may be developed directly as the ratio of dissolved to total recoverable metal; and (3) it may be developed through the use of a partition coefficient that is functionally related to the number of metal binding sites on the adsorbent in the water column (*e.g.,* concentrations of total suspended solids or TSS). This guidance document discusses these three forms of translators, as well as field study designs, data generation and analysis, and site-specific study plans to generate site-specific translators.

California Regional Water Quality Control Boards may use any of these methods in developing water quality-based permit limits to meet water quality standards based on dissolved metals criteria. EPA encourages the State to adopt a statewide policy on the use of translators so that the most appropriate method or methods are used consistently within California.

c. Application of Metals Criteria

In selecting an approach for implementing the metals criteria, the principal issue is the correlation between metals that are measured and metals that are biologically available and toxic. In order to assure that the metals criteria are appropriate for the chemical conditions under which they are applied, EPA is providing for the

adjustment of the criteria through application of the ''water-effect ratio'' procedure. EPA notes that performing the testing to use a site-specific water-effect ratio is optional on the part of the State.

In the NTR, as amended, EPA identified the water-effect ratio (WER) procedure as a method for optional site-specific criteria development for certain metals. The WER approach compares bioavailability and toxicity of a specific pollutant in receiving waters and in laboratory waters. A WER is an appropriate measure of the toxicity of a material obtained in a site water divided by the same measure of the toxicity of the same material obtained simultaneously in a laboratory dilution water.

On February 22, 1994, EPA issued *Interim Guidance on the Determination and Use of the Water-Effect Ratios for Metals* (EPA 823-B–94–001) now incorporated into the updated Second Edition of the Water Quality Standards Handbook, Appendix L. A copy of the Handbook is contained in the administrative record for today's rule. In accordance with the WER guidance and where application of the WER is deemed appropriate, EPA strongly encourages the application of the WER on a watershed or water body basis as part of a water quality criteria in California as opposed to the application on a discharger-by-discharger basis through individual NPDES permits. This approach is technically sound and an efficient use of resources. However, discharger specific WERs for individual NPDES permit limits are possible and potentially efficient where the NPDES discharger is the only point source discharger to a specific water body.

The rule requires a default WER value of 1.0 which will be assumed, if no site-specific WER is determined. To use a WER other than the default of 1.0, the rule requires that the WER must be determined as set forth in EPA's WER guidance or by another scientifically defensible method that has been adopted by the State as part of its water quality standards program and approved by EPA.

The WER is a more comprehensive mechanism for addressing bioavailability issues than simply expressing the criteria in terms of dissolved metal. Consequently, expressing the criteria in terms of dissolved metal, as done in today's rule for California, does not completely eliminate the utility of the WER. This is particularly true for copper, a metal that forms reduced-toxicity complexes with dissolved organic matter.

The *Interim Guidance on Determination and Use of Water-Effect Ratios for Metals* explains the relationship between WERs for dissolved criteria and WERs for total recoverable criteria. Dissolved measurements are to be used in the site-specific toxicity testing underlying the WERs for dissolved criteria. Because WERs for dissolved criteria generally are little affected by elevated particulate concentrations, EPA expects those WERs to be somewhat less than WERs for total recoverable criteria in such situations. Nevertheless, after the site-specific ratio of dissolved to total metal has been taken into account, EPA expects a permit limit derived using a WER for a dissolved criterion to be similar to the permit limit that would be derived from the WER for the corresponding total recoverable criterion.

d. Saltwater Copper Criteria

The saltwater copper criteria for aquatic life in today's rule are 4.8 µg/l (CMC) and 3.1 µg/l (CCC) in the dissolved form. These criteria reflect new data including data collected from studies for the New York/New Jersey Harbor and the San Francisco Bay indicating a need to revise the former copper 304(a) criteria guidance document to reflect a change in the saltwater CMC and CCC aquatic life values. These data also reflect a comprehensive literature search resulting in added toxicity test data for seven new species to the database for the saltwater copper criteria. EPA believes these new data have national implications and the national criteria guidance now contains a CMC of 4.8 µg/l dissolved and a CCC of 3.1 µg/l dissolved. In the amendments to the NTR, EPA noticed the availability of data to support these changes to the NTR, and solicited comments. The data can be found in the draft document entitled, *Ambient Water Quality Criteria—Copper, Addendum 1995.* This document is available from the Office of Water Resource Center and is available for review in the administrative record for today's rule.

e. Chronic Averaging Period

In establishing water quality criteria, EPA generally recommends an ''averaging period'' which reflects the duration of exposure required to elicit effects in individual organisms (TSD, Appendix D–2). The criteria continuous concentration, or CCC, is intended to be the highest concentration that could be maintained indefinitely in a water body without causing an unacceptable effect on the aquatic community or its uses (TSD, Appendix D–1). As aquatic organisms do not generally experience steady exposure, but rather fluctuating exposures to pollutants, and because aquatic organisms can generally tolerate higher concentrations of pollutants over a shorter periods of time, EPA expects that the concentration of a pollutant can exceed the CCC without causing an unacceptable effect if (a) the magnitude and duration of exceedences are appropriately limited and (b) there are compensating periods of time during which the concentration is below the CCC. This is done by specifying a duration of an ''averaging period'' over which the average concentration should not exceed the CCC more often than specified by the frequency (TSD, Appendix D–1).

EPA is promulgating a 4-day averaging period for chronic criteria, which means that measured or predicted ambient pollutant concentrations should be averaged over a 4-day period to determine attainment of chronic criteria. The State may apply to EPA for approval of an alternative averaging period. To do so, the State must submit to EPA the basis for such alternative averaging period.

The most important consideration for setting an appropriate averaging period is the length of time that sensitive organisms can tolerate exposure to a pollutant at levels exceeding a criterion without showing adverse effects on survival, growth, or reproduction. EPA believes that the chronic averaging period must be shorter than the duration of the chronic tests on which the CCC is based, since, in some cases, effects are elicited before exposure of the entire duration. Most of the toxicity tests used to establish the chronic criteria are conducted using steady exposure to toxicants for a least 28 days (TSD, page 35). Some chronic tests, however, are much shorter than this (TSD, Appendix D–2). EPA selected the 4-day averaging period based on the shortest duration in which chronic test effects are sometimes observed for certain species and toxicants. In addition, EPA believes that the results of some chronic tests are due to an acute effect on a sensitive life stage that occurs some time during the test, rather than being caused by long-term stress or long-term accumulation of the test material in the organisms.

Additional discussion of the rationale for the 4-day averaging period is contained in Appendix D of the TSD. Balancing all of the above factors and data, EPA believes that the 4-day averaging period falls within the scientifically reasonable range of values for choice of the averaging period, and is an appropriate length of time of

pollutant exposure to ensure protection of sensitive organisms.

EPA established a 4-day averaging period in the NTR. In settlement of litigation on the NTR, EPA stated that it was ''in the midst of conducting, sponsoring, or planning research related to the basis for and application of'' water quality criteria and mentioned the issue of averaging period. See Partial Settlement Agreement in *American Forest and Paper Ass'n, Inc. et al.* v. *U.S. EPA* (Consolidated Case No. 93–0694 (RMU), D.D.C.). EPA is re-evaluating issues raised about averaging periods and will, if appropriate, revise the 1985 Guidelines.

EPA received public comment relevant to the averaging period during the comment period for the 1995 Amendments to the NTR (60 FR 22228, May 4, 1995), although these public comments did not address the chronic averaging period separately from the allowable excursion frequency and the design flow. Comments recommended that EPA use the 30Q5 design flow for chronic criteria.

While EPA is undertaking analysis of the chronic design conditions as part of the revisions to the 1985 Guidelines, EPA has not yet completed this work. Until this work is complete, for the reasons set forth in the TSD, EPA continues to believe that the 4-day chronic averaging period represents a reasonable, defensible value for this parameter.

EPA added language to the final rule which will enable the State to adopt alternative averaging periods and frequencies and associated design flows where appropriate. The State may apply to EPA for approval of alternative averaging periods and frequencies and related design flows; the State must submit the bases for any changes. Before approving any change, EPA will publish for public comment, a notice proposing the changes.

f. Hardness

Freshwater aquatic life criteria for certain metals are expressed as a function of hardness because hardness and/or water quality characteristics that are usually correlated with hardness can reduce or increase the toxicities of some metals. Hardness is used as a surrogate for a number of water quality characteristics which affect the toxicity of metals in a variety of ways. Increasing hardness has the effect of decreasing the toxicity of metals. Water quality criteria to protect aquatic life may be calculated at different concentrations of hardnesses measured in milligrams per liter (mg/l) as calcium carbonate ($CaCO_3$).

Section 131.38(b)(2) of the final rule presents the hardness-dependent equations for freshwater metals criteria. For example, using the equation for zinc, the total recoverable CMCs at a hardness of 10, 50, 100 or 200 mg/l as $CaCO_3$ are 17, 67, 120 and 220 micrograms per liter (µg/l), respectively. Thus, the specific value in the table in the regulatory text is for illustrative purposes only. Most of the data used to develop these hardness equations for deriving aquatic life criteria for metals were in the range of 25 mg/l to 400 mg/l as $CaCO_3$, and the formulas are therefore most accurate in this range. The majority of surface waters nationwide and in California have a hardness of less than 400 mg/l as $CaCO_3$.

In the past, EPA generally recommended that 25 mg/l as $CaCO_3$ be used as a default hardness value in deriving freshwater aquatic life criteria for metals when the ambient (or actual) hardness value is below 25 mg/l as $CaCO_3$. However, use of the approach results in criteria that may not be fully protective. Therefore, for waters with a hardness of less than 25 mg/l as $CaCO_3$, criteria should be calculated using the actual ambient hardness of the surface water.

In the past, EPA generally recommended that if the hardness was over 400 mg/l, two options were available: (1) Calculate the criterion using a default WER of 1.0 and using a hardness of 400 mg/l in the hardness equation; or (2) calculate the criterion using a WER and the actual ambient hardness of the surface water in the equation. Use of the second option is expected to result in the level of protection intended in the 1985 Guidelines whereas use of the first option is thought to result in an even more protective aquatic life criterion. At high hardness there is an indication that hardness and related inorganic water quality characteristics do not have as much of an effect on toxicity of metals as they do at lower hardnesses. Related water quality characteristics do not correlate as well at higher hardnesses as they do at lower hardnesses. Therefore, if hardness is over 400 mg/l as $CaCO_3$, a hardness of 400 mg/l as $CaCO_3$ should be used with a default WER of 1.0; alternatively, the WER and actual hardness of the surface water may be used.

EPA requested comments in the NTR amendments on the use of actual ambient hardness for calculating criteria when the hardness is below 25 mg/l as $CaCO_3$, and when hardness is greater than 400 mg/l as $CaCO_3$. Most of the comments received were in favor of using the actual hardness with the use of the water-effect ratio (1.0 unless otherwise specified by the permitting authority) when the hardness is greater than 400 mg/l as $CaCO_3$. A few commenters did not want the water-effect ratio to be mandatory in calculating hardness, and other commenters had concerns about being responsible for deriving an appropriate water-effect ratio. Overall, the commenters were in favor of using the actual hardness when calculating hardness-dependent freshwater metals criteria for hardness between 0–400 mg/l as $CaCO_3$. EPA took those comments into account in promulgating today's rule.

A hardness equation is most accurate when the relationships between hardness and the other important inorganic constituents, notably alkalinity and pH, are nearly identical in all of the dilution waters used in the toxicity tests and in the surface waters to which the equation is to be applied. If an effluent raises hardness but not alkalinity and/or pH, using the hardness of the downstream water might provide a lower level of protection than intended by the 1985 guidelines. If it appears that an effluent causes hardness to be inconsistent with alkalinity and/or pH, the intended level of protection will usually be maintained or exceeded if either (1) data are available to demonstrate that alkalinity and/or pH do not affect the toxicity of the metal, or (2) the hardness used in the hardness equation is the hardness of upstream water that does not contain the effluent. The level of protection intended by the 1985 guidelines can also be provided by using the WER procedure.

In some cases, capping hardness at 400 mg/l might result in a level of protection that is higher than that intended by the 1985 guidelines, but any such increase in the level of protection can be overcome by use of the WER procedure. For metals whose criteria are expressed as hardness equations, use of the WER procedure will generally be intended to account for effects of such water quality characteristics as total organic carbon on the toxicities of metals. The WER procedure is equally useful for accounting for any deviation from a hardness equation in a site water.

3. Human Health Criteria

EPA's CWA section 304(a) human health criteria guidance provides criteria recommendations to minimize adverse human effects due to substances in ambient water. EPA's CWA section 304(a) criteria guidance for human health are based on two types of

toxicological endpoints: (1) carcinogenicity and (2) systemic toxicity (i.e., all other adverse effects other than cancer). Thus, there are two procedures for assessing these health effects: one for carcinogens and one for non-carcinogens.

If there are no data on how a chemical agent causes cancer, EPA's existing human health guidelines assume that carcinogenicity is a ''non-threshold phenomenon,'' that is, there are no ''safe'' or ''no-effect levels'' because even extremely small doses are assumed to cause a finite increase in the incidence of the effect (i.e., cancer). Therefore, EPA's water quality criteria guidance for carcinogens are presented as pollutant concentrations corresponding to increases in the risk of developing cancer. See Human Health Guidelines at 45 FR 79347.

With existing criteria, pollutants that do not manifest any apparent carcinogenic effect in animal studies (i.e., systemic toxicants), EPA assumes that the pollutant has a threshold below which no effect will be observed. This assumption is based on the premise that a physiological mechanism exists within living organisms to avoid or overcome the adverse effect of the pollutant below the threshold concentration.

Note: Recent changes in the Agency's cancer guidelines addressing these assumptions are described in the Draft Water Quality Criteria Methodology: Human Health, 63 FR 43756, August 14, 1998.

The human health risks of a substance cannot be determined with any degree of confidence unless dose-response relationships are quantified. Therefore, a dose-response assessment is required before a criterion can be calculated. The dose-response assessment determines the quantitative relationships between the amount of exposure to a substance and the onset of toxic injury or disease. Data for determining dose-response relationships are typically derived from animal studies, or less frequently, from epidemiological studies in exposed populations.

The dose-response information needed for carcinogens is an estimate of the carcinogenic potency of the compound. Carcinogenic potency is defined here as a general term for a chemical's human cancer-causing potential. This term is often used loosely to refer to the more specific carcinogenic or cancer slope factor which is defined as an estimate of carcinogenic potency derived from animal studies or epidemiological data of human exposure. It is based on extrapolation from test exposures of high doses over relatively short periods of time to more realistic low doses over a lifetime exposure period by use of linear extrapolation models. The cancer slope factor, q1*, is EPA's estimate of carcinogenic potency and is intended to be a conservative upper bound estimate (e.g. 95% upper bound confidence limit).

For non-carcinogens, EPA uses the reference dose (RfD) as the dose-response parameter in calculating the criteria. For non-carcinogens, oral RfD assessments (hereinafter simply ''RfDs'') are developed based on pollutant concentrations that cause threshold effects. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. See Human Health Guidelines. The RfD was formerly referred to as an ''Acceptable Daily Intake'' or ADI. The RfD is useful as a reference point for gauging the potential effect of other doses. Doses that are less than the RfD are not likely to be associated with any health risks, and are therefore less likely to be of regulatory concern. As the frequency of exposures exceeding the RfD increases and as the size of the excess increases, the probability increases that adverse effect may be observed in a human population. Nonetheless, a clear conclusion cannot be categorically drawn that all doses below the RfD are ''acceptable'' and that all doses in excess of the RfD are ''unacceptable.'' In extrapolating non-carcinogen animal test data to humans to derive an RfD, EPA divides either a No Observed-Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), or other benchmark dose observed in animal studies by an ''uncertainty factor'' which is based on professional judgment of toxicologists and typically ranges from 10 to 10,000.

For CWA section 304(a) human health criteria development, EPA typically considers only exposures to a pollutant that occur through the ingestion of water and contaminated fish and shellfish. Thus, the criteria are based on an assessment of risks related to the surface water exposure route only where designated uses are drinking water and fish and shellfish consumption.

The assumed exposure pathways in calculating the criteria are the consumption of 2 liters per day of water at the criteria concentration and the consumption of 6.5 grams per day of fish and shellfish contaminated at a level equal to the criteria concentration but multiplied by a ''bioconcentration factor.'' The use of fish and shellfish consumption as an exposure factor requires the quantification of pollutant residues in the edible portions of the ingested species.

Bioconcentration factors (BCFs) are used to relate pollutant residues in aquatic organisms to the pollutant concentration in ambient waters. BCFs are quantified by various procedures depending on the lipid solubility of the pollutant. For lipid soluble pollutants, the average BCF is calculated from the weighted average percent lipids in the edible portions of fish and shellfish, which is about 3%; or it is calculated from theoretical considerations using the octanol/water partition coefficient. For non-lipid soluble compounds, the BCF is determined empirically. The assumed water consumption is taken from the National Academy of Sciences publication *Drinking Water and Health* (1977). (Referenced in the Human Health Guidelines.) This value is appropriate as it includes a margin of safety so that the general population is protected. See also EPA's discussion of the 2.0 liters/day assumption at 61 FR 65183 (Dec. 11, 1996). The 6.5 grams per day contaminated fish and shellfish consumption value was equivalent to the average per-capita consumption rate of all (contaminated and non-contaminated) freshwater and estuarine fish and shellfish for the U.S. population. See Human Health Guidelines.

EPA assumes in calculating water quality criteria that the exposed individual is an average adult with body weight of 70 kilograms. EPA assumes 6.5 grams per day of contaminated fish and shellfish consumption and 2.0 liters per day of contaminated drinking water consumption for a 70 kilogram person in calculating the criteria. Regarding issues concerning criteria development and differences in dose per kilogram of body weight, RfDs are always derived based on the most sensitive health effect endpoint. Therefore, when that basis is due to a chronic or lifetime health effect, the exposure parameters assume the exposed individual to be the average adult, as indicated above.

In the absence of this final rule, there may be particular risks to children. EPA believes that children are protected by the human health criteria contained in this final rule. Children are protected against other less sensitive adverse health endpoints due to the conservative way that the RfDs are derived. An RfD is a public health protective endpoint. It is an amount of a chemical that can be consumed on a daily basis for a lifetime without expecting an adverse effect. RfDs are based on sensitive health endpoints and

are calculated to be protective for sensitive human sub-populations including children. If the basis of the RfD was due to an acute or shorter-term developmental effect, EPA uses exposure parameters other than those indicated above. Specifically, EPA uses parameters most representative of the population of concern (*e.g.,* the health criteria for nitrates based on infant exposure parameters). For carcinogens, the risk assessments are upper bound one in a million (10^{-6}) lifetime risk numbers. The risk to children is not likely to exceed these upper bounds estimates and may be zero at low doses. The exposure assumptions for drinking water and fish protect children because they are conservative for infants and children. EPA assumes 2 liters of untreated surface water and 6.5 grams of freshwater and estuarine fish are consumed each day. EPA believes the adult fish consumption assumption is conservative for children because children generally consume marine fish not freshwater and estuarine.

EPA has a process to develop a scientific consensus on oral reference dose assessments and carcinogenicity assessments (hereinafter simply cancer slope factors or slope factors or q1*s). Through this process, EPA develops a consensus of Agency opinion which is then used throughout EPA in risk management decision-making. EPA maintains an electronic data base which contains the official Agency consensus for oral RfD assessments and carcinogenicity assessments which is known as the Integrated Risk Information System (IRIS). It is available for use by the public on the National Institutes of Health's National Library of Medicine's TOXNET system, and through diskettes from the National Technical Information Service (NTIS). (NTIS access number is PB 90–591330.)

Section 304(a)(1) of the CWA requires EPA to periodically revise its criteria guidance to reflect the latest scientific knowledge: ''(A) On the kind and extent of all identifiable effects on health and welfare * * *; (B) on the concentration and dispersal of pollutants, or their byproducts, through biological, physical, and chemical processes; and (C) on the effects of pollutants on the biological community diversity, productivity, and stability, including information on the factors affecting eutrophication rates of organic and inorganic sedimentation for varying types of receiving waters.'' In developing up-to-date water quality criteria for the protection of human health, EPA uses the most recent IRIS values (RfDs and q1*s) as the toxicological basis in the criterion calculation. IRIS reflects EPA's most current consensus on the toxicological assessment for a chemical. In developing the criteria in today's rule, the IRIS values as of October 1996 were used together with currently accepted exposure parameters for bioconcentration, fish and shellfish and water consumption, and body weight. The IRIS cover sheet for each pollutant criteria included in today's rule is contained in the administrative record.

For the human health criteria included in today's rule, EPA used the Human Health Guidelines on which criteria recommendations from the appropriate CWA section 304(a) criteria guidance document were based. (These documents are also placed in the administrative record for today's rule.) Where EPA has changed any parameters in IRIS used in criteria derivation since issuance of the criteria guidance document, EPA recalculated the criteria recommendation with the latest IRIS information. Thus, there are differences between the original 1980 criteria guidance document recommendations, and those in this rule, but this rule presents EPA's most current CWA section 304(a) criteria recommendation. The basis (q1* or RfD) and BCF for each pollutant criterion in today's rule is contained in the rule's Administrative Record Matrix which is included in the administrative record for the rule. In addition, all recalculated human health numbers are denoted by an ''a'' in the criteria matrix in 40 CFR 131.38(b)(1) of the rule. The pollutants for which a revised human health criterion has been calculated since the December 1992 NTR include:

mercury
dichlorobromomethane
1,2-dichloropropane
1,2-trans-dichloroethylene
2,4-dimethylphenol
acenaphthene
benzo(a)anthracene
benzo(a)pyrene
benzo(b)flouranthene
benzo(k)flouranthene
2-chloronaphthalene
chrysene
dibenzo(a,h)anthracene
indeno(1,2,3-cd)pyrene
N-nitrosodi-n-propylamine
alpha-endosulfan
beta-endosulfan
endosulfan sulfate
2-chlorophenol
butylbenzyl phthalate
polychlorinated biphenyls.

In November of 1991, the proposed NTR presented criteria for several pollutants in parentheses. These were pollutants for which, in 1980, insufficient information existed to develop human health water quality criteria, but for which, in 1991, sufficient information existed. Since these criteria did not undergo the public review and comment in a manner similar to the other water quality criteria presented in the NTR (for which sufficient information was available in 1980 to develop a criterion, as presented in the 1980 criteria guidance documents), they were not proposed for adoption into the water quality criteria, but were presented to serve as notice for inclusion in future State triennial reviews. Today's rule promulgates criteria for these nine pollutants:

copper
1, 2-dichloropropane
1,2-trans-dichloroethylene
2,4-dimethylphenol
acenaphthene
2-chloronaphthalene
N-nitrosodi-n-propylamine
2-chlorophenol
butylbenzene phthalate

All the criteria are based on IRIS values—either an RfD or q1*—which were listed on IRIS as of November 1991, the date of the proposed NTR. These values have not changed since the final NTR was published in December of 1992. The rule's Administrative Record Matrix in the administrative record of today's rule contains the specific RfDs, q1*s, and BCFs used in calculating these criteria.

Proposed Changes to the Human Health Criteria Methodology: EPA recently proposed revisions to the 1980 ambient water quality criteria derivation guidelines (the Human Health Guidelines). See *Draft Water Quality Criteria Methodology: Human Health,* 63 FR 43756, August 14, 1998; see also *Draft Water Quality Criteria Methodology: Human Health,* U.S. EPA Office of Water, EPA 822–Z–98–001. The EPA revisions consist of five documents: *Draft Water Quality Criteria Methodology: Human Health,* EPA 822–Z–98–001; *Ambient Water Quality Criteria Derivation Methodology Human Health, Technical Support Document, Final Draft,* EPA–822–B–98–005; and three Ambient Water Quality Criteria for the Protection of Human Health, Drafts—one each for Acrylonitrile, 1,3-Dichloropropene (1,3-DCP), and Hexachlorobutadiene (HCBD), respectively, EPA–822–R–98–006, –005, and –004. All five documents are contained in the administrative record for today's rule.

The proposed methodology revisions reflect significant scientific advances that have occurred during the past nineteen years in such key areas as cancer and noncancer risk assessments, exposure assessments and bioaccumulation. For specific details on

these proposed changes and others, please refer to the **Federal Register** notice or the EPA document.

It should be noted that some of the proposed changes may result in significant numeric changes in the ambient water quality criteria. However, EPA will continue to rely on existing criteria as the basis for regulatory and non-regulatory decisions, until EPA revises and reissues a 304(a) criteria guidance using the revised final human health criteria methodology. The existing criteria are still viewed as scientifically acceptable by EPA. The intention of the proposed methodology revisions is to present the latest scientific advancements in the areas of risk and exposure assessment in order to incrementally improve the already sound toxicological and exposure bases for these criteria. As EPA's current human health criteria are the product of many years worth of development and peer review, it is reasonable to assume that revisiting all existing criteria, and incorporating peer review into such review, could require comparable amounts of time and resources. Given these circumstances, EPA proposed a process for revisiting these criteria as part of the overall revisions to the methodology for deriving human health criteria. This process is discussed in the Implementation Section of the Notice of *Draft Revisions to the Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (see 63 FR 43771–43776, August 14, 1998).

The State of California in its Ocean Plan, adopted in 1990 and approved by EPA in 1991, established numeric water quality criteria using an average fish and shellfish consumption rate of 23 grams per day. This value is based on an earlier California Department of Health Services estimate. The State is currently in the process of readopting its water quality control plans for inland surface waters, enclosed bays, and estuaries. The State intends to consider information on fish and shellfish consumption rates evaluated and summarized in a report prepared by the State's Pesticide and Environmental Toxicology Section of the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency. The report, entitled, *Chemicals in Fish Report No. 1: Consumption of Fish and Shellfish in California and the United States,* was published in final draft form in July of 1997, and released to the public on September 16, 1997. The report is currently undergoing final evaluation, and is expected to published in final form in the near future. This final draft report is contained in the administrative record for today's rule. Although EPA has not used this fish consumption value here because this information has not yet been finalized, the State may use any appropriate higher state-specific fish and shellfish consumption rates in its readoption of criteria in its statewide plans.

a. 2,3,7,8-TCDD (Dioxin) Criteria

In today's action, EPA is promulgating human health water quality criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin (''dioxin'') at the same levels as promulgated in the NTR, as amended. These criteria are derived from EPA's 1984 CWA section 304(a) criteria guidance document for dioxin.

For National Pollutant Discharge Elimination System (NPDES) purposes, EPA supports the regulation of other dioxin and dioxin-like compounds through the use of toxicity equivalencies or TEQs in NPDES permits (see discussion below). For California waters, if the discharge of dioxin or dioxin-like compounds has reasonable potential to cause or contribute to a violation of a narrative criterion, numeric water quality-based effluent limits for dioxin or dioxin-like compounds should be included in NPDES permits and should be expressed using a TEQ scheme.

EPA has been evaluating the health threat posed by dioxin nearly continuously for over two decades. Following issuance of the 1984 criteria guidance document, evaluating the health effects of dioxin and recommending human health criteria for dioxin, EPA prepared draft reassessments reviewing new scientific information relating to dioxin in 1985 and 1988. EPA's Science Advisory Board (SAB), reviewing the 1988 draft reassessment, concluded that while the risk assessment approach used in 1984 criteria guidance document had inadequacies, a better alternative was unavailable (see SAB's *Dioxin Panel Review of Documents from the Office or Research and Development relating to the Risk and Exposure Assessment of 2,3,7,8-TCDD* (EPA–SAB–EC–90–003, November 28, 1989) included in the administrative record for today's rule). Between 1988 and 1990, EPA issued numerous reports and guidances relating to the control of dioxin discharges from pulp and paper mills. See e.g., EPA Memorandum, ''Strategy for the Regulation of Discharges of PHDDs & PHDFs from Pulp and Paper Mills to the Waters of the United States,'' from Assistant Administrator for Water to Regional Water Management Division Directors and NPDES State Directors, dated May 21, 1990 (AR NL–16); EPA Memorandum, ''State Policies, Water Quality Standards, and Permit Limitations Related to 2,3,7,8-TCDD in Surface Water,'' from the Assistant Administrator for Water to Regional Water Management Division Directors, dated January 5, 1990 (AR VA–66). These documents are available in the administrative record for today's rule.

In 1991, EPA's Administrator announced another scientific reassessment of the risks of exposure to dioxin (see Memorandum from Administrator William K. Reilly to Erich W. Bretthauer, Assistant Administrator for Research and Development and E. Donald Elliott, General Counsel, entitled *Dioxin: Follow-Up to Briefing on Scientific Developments,* April 8, 1991, included in the administrative record for today's rule). At that time, the Administrator made clear that while the reassessment was underway, EPA would continue to regulate dioxin in accordance with existing Agency policy. Thereafter, the Agency proceeded to regulate dioxin in a number of environmental programs, including standards under the Safe Drinking Water Act and the CWA.

The Administrator's promulgation of the dioxin human health criteria in the 1992 NTR affirmed the Agency's decision that the ongoing reassessment should not defer or delay regulating this potent contaminant, and further, that the risk assessment in the 1984 criteria guidance document for dioxin continued to be scientifically defensible. Until the reassessment process was completed, the Agency could not ''say with any certainty what the degree or directions of any changes in the risk estimates might be'' (57 FR 60863–64).

The basis for the dioxin criteria as well as the decision to include the dioxin criteria in the 1992 NTR pending the results of the reassessment were challenged. See *American Forest and Paper Ass'n, Inc. et al.* v. *U.S. EPA* (Consolidated Case No. 93–0694 (RMU) D.D.C.). By order dated September 4, 1996, the Court upheld EPA's decision. EPA's brief and the Court's decision are included in the administrative record for today's rule.

EPA has undertaken significant effort toward completion of the dioxin reassessment. On September 13, 1994, EPA released for public review and comment a draft reassessment of toxicity and exposure to dioxin. See *Health Assessment Document for 2,3,7,8-Tetrachlorobenzo-p-Dioxin (TCDD) and Related Compounds,* U.S. EPA, 1994. EPA is currently addressing comments made by the public and the SAB and anticipates that the final

revised reassessment will go to the SAB in the near future. With today's rule, the Agency reaffirms that, notwithstanding the on-going risk reassessment, EPA intends to continue to regulate dioxin to avoid further harm to public health, and the basis for the dioxin criteria, both in terms of the cancer potency and the exposure estimates, remains scientifically defensible. The fact that EPA is reassessing the risk of dioxin, virtually a continuous process to evaluate new scientific information, does not mean that the current risk assessment is ''wrong''. It continues to be EPA's position that until the risk assessment for dioxin is revised, EPA supports and will continue to use the existing risk assessment for the regulation of dioxin in the environment. Accordingly, EPA today promulgates dioxin criteria based on the 1984 criteria guidance document for dioxin and promulgated in the NTR in 1992.

Toxicity Equivalency: The State of California, in its 1991 water quality control plans, adopted human health criteria for dioxin and dioxin-like compounds based on the concept of toxicity equivalency (TEQ) using toxicity equivalency factors (TEFs). EPA Region 9 reviewed and approved the State's use of the TEQ concept and TEFs in setting the State's human health water quality criteria for dioxin and dioxin-like compounds.

In 1987, EPA formally embraced the TEQ concept as an interim procedure to estimate the risks associated with exposures to 210 chlorinated dibenzo-p-dioxin and chlorinated dibenzofuran (CDD/CDF) congeners, including 2,3,7,8-TCDD. This procedure uses a set of derived TEFs to convert the concentration of any CDD/CDF congener into an equivalent concentration of 2,3,7,8-TCDD. In 1989, EPA updated its TEFs based on an examination of relevant scientific evidence and a recognition of the value of international consistency. This updated information can be found in EPA's 1989 *Update to the Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-dioxins and -dibenzofurans (CDDs and CDFs)* (EPA/625/3–89/016, March 1989). EPA had been active in an international effort aimed at adopting a common set of TEFs (International TEFs/89 or I–TEFs/89), to facilitate information exchange on environmental contamination of CDD/CDF. This document reflects EPA's support of an internationally consistent set of TEFs, the I–TEFs/89. EPA uses I–TEFs/89 in many of its regulatory programs.

In 1994, the World Health Organization (WHO) revised the TEF scheme for dioxins and furans to include toxicity from dioxin-like compounds (Ahlborg et al., 1994). However, no changes were made to the TEFs for dioxins and furans. In 1998, the WHO re-evaluated and revised the previously established TEFs for dioxins (Ds), furans (Fs) and dioxin-like compounds (Vanden Bers, 1998). The nomenclature for this TEF scheme is TEQDFP–WHO98, where TEQ represents the 2,3,7,8-TCDD Toxic Equivalence of the mixture, and the subscript DFP indicates that dioxins (Ds) furans (Fs) and dioxin-like compounds (P) are included in the TEF scheme. The subscript 98 following WHO displays the year changes were made to the TEF scheme.

EPA intends to use the 1998 WHO TEF scheme in the near future. At this point however, EPA will support the use of either the 1989 interim procedures or the 1998 WHO TEF scheme but encourages the use of the 1998 WHO TEF scheme in State programs. EPA expects California to use a TEF scheme in implementing the 2,3,7,8-TCDD water quality criteria contained in today's rule. The TEQ and TEF approach provide a methodology for setting NPDES water quality-based permit limits that are protective of human health for dioxin and dioxin-like compounds.

Several commenters requested EPA to promulgate criteria for other forms of dioxin, in addition to 2,3,7,8-TCDD. EPA's draft reassessment for dioxin examines toxicity based on the TEQ concept and I–TEFs/89. When EPA completes the dioxin reassessment, the Agency intends to adopt revised 304(a) water quality criteria guidance based on the reassessment for dioxin. If necessary, EPA will then act to amend the NTR and CTR to reflect the revised 304(a) water quality criteria guidance.

b. Arsenic Criteria

EPA is not promulgating human health criteria for arsenic in today's rule. EPA recognizes that it promulgated human health water quality criteria for arsenic for a number of States in 1992, in the NTR, based on EPA's 1980 section 304(a) criteria guidance for arsenic established, in part, from IRIS values current at that time. However, a number of issues and uncertainties existed at the time of the CTR proposal concerning the health effects of arsenic. These issues and uncertainties were summarized in ''Issues Related to Health Risk of Arsenic'' which is contained in the administrative record for today's rule. During the period of this rulemaking action, EPA commissioned a study of arsenic health effects by the National Research Council (NRC) arm of the National Academy of Sciences. EPA received the NRC report in March of 1999. EPA scientists reviewed the report, which recommended that EPA lower the Safe Drinking Water Act arsenic maximum contaminant level (MCL) as soon as possible (The arsenic MCL is currently 50 μg/l.) The bladder cancer analysis in the NRC report will provide part of the basis for the risk assessment of a proposed revised arsenic MCL in the near future. After promulgating a revised MCL for drinking water, the Agency plans to revise the CWA 304(a) human health criteria for arsenic in order to harmonize the two standards. Today's rule defers promulgating arsenic criteria based on the Agency's previous risk assessment of skin cancer. In the meantime, permitting authorities in California should rely on existing narrative water quality criteria to establish effluent limitations as necessary for arsenic. California has previously expressed its science and policy position by establishing a criterion level of 5 μg/l for arsenic. Permitting authorities may, among other considerations, consider that value when evaluating and interpreting narrative water quality criteria.

c. Mercury Criteria

The human health criteria promulgated here use the latest RfD in EPA's Integrated Risk Information System (IRIS) and the weighted average practical bioconcentration factor (PBCF) from the 1980 section 304(a) criteria guidance document for mercury. EPA considered the approach used in the Great Lakes Water Quality Guidance (''Guidance'') incorporating Bioaccumulation Factors (BAFs), but rejected this approach for reasons outlined below. The equation used here to derive an ambient water quality criterion for mercury from exposure to organisms and water is:

$$HHC = \frac{RfD \times BW}{WC + (FC \times PBCF)}$$

Where:

RfD = Reference Dose
BW = Body Weight
WC = Water Consumption
FC = Total Fish and Shellfish Consumption per Day
PBCF = Practical Bioconcentration Factor (weighted average)

For mercury, the most current RfD from IRIS is 1×10^{-4} mg/kg/day. The RfD used a benchmark dose as an estimate of a No Observed Adverse Effect Level (NOAEL). The benchmark dose was calculated by applying a Weibel model

for extra risk to all neurological effects observed in 81 Iraqi children exposed in utero as reported in Marsh, et. al. (1987). Maternal hair mercury was the measure of exposure. Extra risk refers to an adjustment for background incidence of a given health effect. Specifically, the extra risk is the added incidence of observing an effect above the background rate relative to the proportion of the population of interest that is not expected to exhibit such as effect. The resulting estimate was the lower 95% statistical bound on the 10% extra risk; this was 11 ppm mercury in maternal hair. This dose in hair was converted to an equivalent ingested amount by applying a model based on data from human studies; the resulting benchmark dose was 1×10^{-3} mg/kg body weight /day. The RfD was calculated by dividing the benchmark dose by a composite uncertainty factor of 10. The uncertainty factor was used to account for variability in the human population, in particular the wide variation in biological half-life of methylmercury and the variation that is observed in the ration of hair mercury to mercury in the blood. In addition the uncertainty factor accounts for lack of a two-generation reproductive study and the lack of data on long term effects of childhood mercury exposures. The RfD thus calculated is 1×10^{-4} mg/kg body weight/day or 0.1 μg/kg/day. The body weight used in the equation for the mercury criteria, as discussed in the Human Health Guidelines, is a mean adult human body weight of 70 kg. The drinking water consumption rate, as discussed in the Human Health Guidelines, is 2.0 liters per day.

The bioconcentration factor or BCF is defined as the ratio of chemical concentration in the organism to that in surrounding water. Bioconcentration occurs through uptake and retention of a substance from water only, through gill membranes or other external body surfaces. In the context of setting exposure criteria it is generally understood that the terms ''BCF'' and ''steady-state BCF'' are synonymous. A steady-state condition occurs when the organism is exposed for a sufficient length of time that the ratio does not change substantially.

The BCFs that were used herein are the ''Practical Bioconcentration Factors (PBCFs)'' that were derived in 1980: 5500 for fresh water, 3765 for estuarine coastal waters, and 9000 for open oceans. See pages C–100–1 of Ambient Water Quality Criteria for Mercury (EPA 440/5–80–058) for a complete discussion on the PBCF. Because of the way they were derived, these PBCFs take into account uptake from food as well as uptake from water. A weighted average PBCF was calculated to take into account the average consumption from the three waters using the following equation:

$$\text{Weighted Average Practical BCF} = \frac{\sum(\text{FC} \times \text{PBCF})}{\sum(\text{FC})} = \frac{(0.00172)(5500) + (0.00478)(3765) + (0.0122)(9000)}{0.00172 + 0.00478 + 0.0122} = \frac{137.3}{0.0187} = 7342.6$$

Given the large value for the weighted average PBCF, the contribution of drinking water to total daily intake is negligible so that assumptions concerning the chemical form of mercury in drinking water become less important. The human health mercury criteria promulgated for this rule are based on the latest RfD as listed in IRIS and a weighted PBCF from the 1980 § 304(a) criteria guidance document for mercury.

On March 23, 1995 (60 FR 15366), EPA promulgated the Great Lakes Water Quality Guidance (''Guidance''). The Guidance incorporated bioaccumulation factors (BAFs) in the derivation of criteria to protect human health because it is believed that BAFs are a better predictor than BCFs of the concentration of a chemical within fish tissue since BAFs include consideration of the uptake of contaminants from all routes of exposure. A bioaccumulation factor is defined as the ratio (in L/kg) of a substance's concentration in tissue to the concentration in the ambient water, in situations where both the organism and its food are exposed and the ratio does not change substantially over time. The final Great Lakes Guidance establishes a hierarchy of four methods for deriving BAFs for non-polar organic chemicals: (1) Field-measured BAFs; (2) predicted BAFs derived using a field-measured biota-sediment accumulation factor; (3) predicted BAFs derived by multiplying a laboratory-measured BCF by a food chain multiplier; and (4) predicted BAFs derived by multiplying a BCF calculated from the log Kow by a food-chain multiplier. The final Great Lakes Guidance developed BAFs for trophic levels three and four fish of the Great Lakes Basin. Respectively, the BAFs for mercury for trophic level 3 and 4 fish were: 27,900 and 140,000.

The BAF promulgated in the GLI was developed specifically for the Great Lakes System. It is uncertain whether the BAFs of 27,900 and 140,000 are appropriate for use in California at this time; therefore, today's final rule does not use the GLI BAF in establishing human health criteria for mercury in California. The magnitude of the BAF for mercury in a given system depends on how much of the total mercury is present in the methylated form. Methylation rates vary widely from one water body to another for reasons that are not fully understood. Lacking the data, it is difficult to determine if the BAF used in the GLI represents the true potential for mercury to bioaccumulate in California surface waters. The true, average BAF for California could be higher or lower. For more information see EPA's Response to Comments document in the administrative record for this rule (specifically comments CTR–002–007(b) and CTR–016–007).

EPA is developing a national BAF for mercury as part of revisions to its 304(a) criteria for human health; however, the BAF methodology that will be used is currently under evaluation as part of EPA's revisions to its National Human Health Methodology (see section F.3 above). EPA applied a similar methodology in its Mercury Study Report to Congress (MSRC) to derive a BAF for methylmercury. The MSRC is available through NTIS (EPA–452/R–97–003). Although a BAF was derived in the MSRC, EPA does not intend to use this BAF for National application. EPA is engaged in a separate effort to incorporate additional mercury bioaccumulation data that was not considered in the MSRC, and to assess uncertainties with using a National BAF approach for mercury. Once the proposed revised human health methodology, including the BAF component, is finalized, EPA will revise its 304(a) criteria for mercury to reflect changes in the underlying methodology, recommendations contained in the MSRC, and recommendations in a National Academy of Science report on human health assessment of methylmercury. When EPA changes its 304(a) criteria recommendation for mercury, States and Tribes will be expected to review their water quality standards for mercury and make any revisions necessary to ensure their standards are scientifically defensible.

New information may become available regarding the bioaccumulation

of mercury in certain water bodies in California. EPA supports the use of this information to develop site-specific criteria for mercury. Further, if a California water body is impaired due to mercury fish tissue or sediment contamination, loadings of mercury could contribute to or exacerbate the impairment. Therefore, one option regulatory authorities should consider is to include water quality-based effluent limits (WQBELs) in permits based on mass for discharges to the impaired water body. Such WQBELs must be derived from and comply with applicable State water quality standards (including both numeric and narrative criteria) and assure that the discharge does not cause or contribute to a violation of water quality standards.

d. Polychlorinated Biphenyls (PCBs) Criteria

The NTR, as amended, calculated human health criteria for PCBs using a cancer potency factor of 7.7 per mg/kg-day from the Agency's IRIS. This cancer potency factor was derived from the Norback and Weltman (1985) study which looked at rats that were fed Aroclor 1260. The study used the linearized multistage model with a default cross-species scaling factor (body weight ratio to the ⅔ power). Although it is known that PCB mixtures vary greatly as to their potency in producing biological effects, for purposes of its carcinogenicity assessment, EPA considered Aroclor 1260 to be representative of all PCB mixtures. The Agency did not pool data from all available congener studies or generate a geometric mean from these studies, since the Norback and Weltman study was judged by EPA as acceptable, and not of marginal quality, in design or conduct as compared with other studies. Thereafter, the Institute for Evaluating Health Risks (IEHR, 1991) reviewed the pathological slides from the Norback and Weltman study, and concluded that some of the malignant liver tumors should have been interpreted as nonmalignant lesions, and that the cancer potency factor should be 5.1 per mg/kg-day as compared with EPA's 7.7 per mg/kg-day.

The Agency's peer-reviewed reassessment of the cancer potency of PCBs published in a final report, *PCBs: Cancer Dose-Response Assessment and Applications to Environmental Mixtures* (EPA/600/P–96/001F), adopts a different approach that distinguishes among PCB mixtures by using information on environmental processes. (The report is included in the administrative record of today's rule.) The report considers all cancer studies (which used commercial mixtures only) to develop a range of cancer potency factors, then uses information on environmental processes to provide guidance on choosing an appropriate potency factor for representative classes of environmental mixtures and different pathways. The reassessment provides that, depending on the specific application, either central estimates or upper bounds can be appropriate. Central estimates describe a typical individual's risk, while upper bounds provide assurance (*i.e.,* 95% confidence) that this risk is not likely to be underestimated if the underlying model is correct. Central estimates are used for comparing or ranking environmental hazards, while upper bounds provide information about the precision of the comparison or ranking. In the reassessment, the use of the upper bound values were found to increase cancer potency estimates by two or three-fold over those using central tendency. Upper bounds are useful for estimating risks or setting exposure-related standards to protect public health, and are used by EPA in quantitative cancer risk assessment. Thus, the cancer potency of PCB mixtures is determined using a tiered approach based on environmental exposure routes with upper-bound potency factors (using a body weight ratio to the ¾ power) ranging from 0.07 (lowest risk and persistence) to 2 (high risk and persistence) per mg/kg-day for average lifetime exposures to PCBs. It is noteworthy that bioaccumulated PCBs appear to be more toxic than commercial PCBs and appear to be more persistent in the body. For exposure through the food chain, risks can be higher than other exposures.

EPA issued the final reassessment report on September 27, 1996, and updated IRIS to include the reassessment on October 1, 1996. EPA updated the human health criteria for PCBs in the National Toxics Rule on September 27, 1999. For today's rule, EPA derived the human health criteria for PCBs using a cancer potency factor of 2 per mg/kg-day, an upper bound potency factor reflecting high risk and persistence. This decision is based on recent multimedia studies indicating that the major pathway of exposure to persistent toxic substances such as PCBs is via dietary exposure (*i.e.,* contaminated fish and shellfish consumption).

Following is the calculation of the human health criterion (HHC) for organism and water consumption:

$$HHC = \frac{RF \times BW \times (1{,}000\ \mu g/mg)}{q1^* \times [WC + (FC \times BCF)]}$$

Where:

RF = Risk Factor = 1 x 10^{-6}
BW = Body Weight = 70 kg
q1* = Cancer slope factor = 2 per mg/kg-day
WC = Water Consumption = 2 l/day
FC = Fish and Shellfish Consumption = 0.0065 kg/day
BCF = Bioconcentration Factor = 31,200

the HHC (μg/l) = 0.00017 μg/l (rounded to two significant digits).

Following is the calculation of the human health criterion for organism only consumption:

$$HHC = \frac{RF \times BW \times (1{,}000\ \mu g/mg)}{q1^* \times FC \times BCF}$$

Where:

RF = Risk Factor = 1 x 10^{-6}
BW = Body Weight = 70 kg
q1* = Cancer slope factor = 2 per mg/kg-day
FC = Total Fish and Shellfish Consumption per Day = 0.0065 kg/day
BCF = Bioconcentration Factor = 31,200

the HHC (μg/l) = 0.00017 μg/l (rounded to two significant digits).

The criteria are both equal to 0.00017 μg/l and apply to total PCBs. *See PCBs: Cancer Dose Response Assessment and Application to Environmental Mixtures* (EPA/600/9–96–001F). For a discussion of the body weight, water consumption, and fish and shellfish consumption factors, see the Human Health Guidelines. For a discussion of the BCF, see the 304(a) criteria guidance document for PCBs (included in the administrative record for today's rule).

e. Excluded Section 304(a) Human Health Criteria

As is the case in the NTR, as amended, today's rule does not promulgate criteria for certain priority pollutants for which CWA section 304(a) criteria guidance exists because those criteria were not based on toxicity to humans or aquatic organisms. The basis for those particular criteria is organoleptic effects (*e.g.,* taste and odor) which would make water and edible aquatic life unpalatable but not toxic. Because the basis for this rule is to protect the public health and aquatic life from toxicity consistent with the language and intent in CWA section 303(c)(2)(B), EPA is promulgating criteria only for those priority toxic pollutants whose criteria recommendations are based on toxicity. The CWA section 304(a) human health criteria based on organoleptic effects for zinc and 3-methyl-4-chlorophenol are excluded for this reason. See the 1992 NTR discussion at 57 FR 60864.

f. Cancer Risk Level

EPA's CWA section 304(a) criteria guidance documents for priority toxic pollutants that are based on carcinogenicity present concentrations for upper bound risk levels of 1 excess cancer case per 100,000 people (10^{-5}), per 1,000,000 people (10^{-6}), and per 10,000,000 people (10^{-7}). However, the criteria documents do not recommend a particular risk level as EPA policy.

As part of the proposed rule, EPA requested and received comment on the adoption of a 10^{-5} risk level for carcinogenic pollutants. The effect of a 10^{-5} risk level would have been to increase (*i.e.,* make less stringent) carcinogenic pollutant criteria values (noted in the matrix by footnote c) that are not already promulgated in the NTR, by one order of magnitude. For example, the organism-only criterion for gamma BHC (pollutant number 105 in the matrix) is 0.013 µg/l; the criterion based on a 10^{-5} risk level would have been 0.13 µg/l. EPA received several comments that indicated a preference for a higher (10^{-4} and 10^{-5}) risk level for effluent dependent waters or other types of special circumstances.

In today's rule, EPA is promulgating criteria that protect the general population at an incremental cancer risk level of one in a million (10^{-6}) for all priority toxic pollutants regulated as carcinogens, consistent with the criteria promulgated in the NTR for the State of California. Standards adopted by the State contained in the Enclosed Bays and Estuaries Plan (EBEP), and the Inland Surface Waters Plan (ISWP), partially approved by EPA on November 6, 1991, and the Ocean Plan approved by EPA on June 28, 1990, contained a risk level of 10^{-6} for most carcinogens. The State has historically protected at a 10^{-6} risk level for carcinogenic pollutants.

EPA, in its recent human health methodology revisions, proposed acceptable lifetime cancer risk for the general population in the range of 10^{-5} to 10^{-6}. EPA also proposed that States and Tribes ensure the most highly exposed populations do not exceed a 10^{-4} risk level. However, EPA's draft methodology revisions also stated that it will derive 304(a) criteria at a 10^{-6} risk level, which the Agency believes reflects the appropriate risk for the general population and which applies a risk management policy which ensures protection for all exposed population groups. (Draft Water Quality Criteria Methodology: Human Health, EPA 822–Z–98–001, August 1998, Appendix II, page 72).

Subpopulations within a State may exist, such as recreational and subsistence anglers, who as a result of greater exposure to a contaminant are at greater risk than the standard 70 kilogram person eating 6.5 grams per day of fish and shellfish and drinking 2.0 liters per day of drinking water with pollutant levels meeting the water quality criteria. EPA acknowledges that at any given risk level for the general population, those segments of the population that are more highly exposed face a higher relative risk. For example, if fish are contaminated at a level permitted by criteria derived on the basis of a risk level of 10^{-6}, individuals consuming up to 10 times the assumed fish consumption rate would still be protected at a 10^{-5} risk level. Similarly, individuals consuming 100 times the general population rate would be protected at a 10^{-4} risk level. EPA, therefore, believes that derivation of criteria at the 10^{-6} risk level is a reasonable risk management decision protective of designated uses under the CWA. While outside the scope of this rule, EPA notes that States and Tribes, however, have the discretion to adopt water quality criteria that result in a higher risk level (*e.g.,* 10^{-5}). EPA expects to approve such criteria if the State or Tribe has identified the most highly exposed subpopulation within the State or Tribe, demonstrates the chosen risk level is adequately protective of the most highly exposed subpopulation, and has completed all necessary public participation.

This demonstration has not happened in California. Further, the information that is available on highly exposed subpopulations in California supports the need to protect the general population at the 10^{-6} level. California has cited the Santa Monica Bay Seafood Consumption Study as providing the best available data set for estimating consumption of sport fish and shellfish in California for both marine or freshwater sources (Chemicals in Fish Report No. 1: Consumption of Fish and Shellfish in California and the United States, Final Draft Report, July 1997). Consumption rates of sport fish and shellfish of 21g/day, 50 g/day, 107 g/day, and 161 g/day for the median, mean, 90th, and 95th percentile rates, respectively, were determined from this study. Additional consumption of commercial species in the range of approximately 8 to 42 g/day would further increase these values. Clearly the consumption rates for the most highly exposed subpopulation within the State exceeds 10 times the 6.5 g/day rates used in the CTR. Therefore, use of a risk level of 10^{-5} for the general population would not be sufficient to protect the most highly exposed population in California at a 10^{-4} risk level. On the other hand, even the most highly exposed subpopulations cited in the California study do not have consumption rates approaching 100 times the 6.5 g/day rates used in the CTR. The use of the 10^{-6} risk level to protect average level consumers does not subject these subpopulations to risk levels as high as 10^{-4}.

EPA believes its decision to establish a 10^{-6} risk level for the CTR is also consistent with EPA's policy in the NTR to select the risk level that reflect the policies or preferences of CWA programs in the affected States. California adopted standards for priority toxic pollutants for its ocean waters in 1990 using a 10^{-6} risk level to protect human health (California Ocean Plan, 1990). In April 1991, and again in November 1992, California adopted standards for its inland surface waters and enclosed bays and estuaries in its Inland Surface Waters Plan (ISWP) and its Enclosed Bays and Estuaries Plan (EBEP) using a 10^{-6} risk level. To be consistent with the State's water quality standards, EPA used a 10^{-6} risk level for California in the NTR at 57 FR 60867. The State has continued using a 10^{-6} risk level to protect human health for its standards that were not withdrawn with the ISWP and EBEP. The most recent expression of risk level preference is contained in the Draft Functional Equivalent Document, Amendment of the Water Quality Control Plan for Ocean Waters of California, October 1998, where the State recommended maintaining a consistent risk level of 10^{-6} for the human health standards that it was proposing to revise.

EPA received several comments requesting a 10^{-5} risk level based on the risk level chosen for the Great Lakes Water Quality Guidance (the Guidance). There are several differences between the guidelines for the derivation of human health criteria contained in the Guidance and the California Toxics Rule (CTR) that make a 10^{-5} risk factor appropriate for the Guidance, but not for the CTR. These differences result in criteria developed using the 10^{-5} risk factor in the Guidance being at least as stringent as criteria derived under the CTR using a 10^{-6} risk factor. The relevant aspects of the Guidance include:

- Use of fish consumption rates that are considerably higher than fish consumption rates for the CTR.
- Use of bioaccumulation factors rather than bioconcentration factors in

estimating exposure, considerably increasing the dose of carcinogens to sensitive subgroups.

• Consideration of additivity of effects of mixtures for both carcinogenic and noncarcinogenic pollutants.

This combination of factors increase the calculated carcinogenic risk substantially under the Guidance (the combination would generally be more than one order of magnitude), making a lower overall risk factor acceptable. The Guidance risk factor provides, in fact, criteria with at least the same level of protection against carcinogens as criteria derived with a higher risk factor using the CTR. A lower risk factor for the CTR would not be appropriate absent concomitant changes in the derivation procedures that provide equivalent risk protection.

G. Description of Final Rule

1. Scope

Paragraph (a) in 40 CFR 131.38, entitled ''Scope,'' states that this rule is a promulgation of criteria for priority toxic pollutants in the State of California for inland surface waters, enclosed bays, and estuaries. Paragraph (a) in 40 CFR 131.38 also states that this rule contains an authorizing compliance schedule provision.

2. EPA Criteria for Priority Toxic Pollutants

EPA's criteria for California are presented in tabular form at 40 CFR 131.38. For ease of presentation, the table that appears combines water quality criteria promulgated in the NTR, as amended, that are outside the scope of this rulemaking, with the criteria that are within the scope of today's rule. This is intended to help readers determine applicable water quality criteria for the State of California. The table contains footnotes for clarification.

Paragraph (b) in 40 CFR 131.38 presents a matrix of the applicable EPA aquatic life and/or human health criteria for priority toxic pollutants in California. Section 303(c)(2)(B) of the CWA addresses only pollutants listed as ''toxic'' pursuant to section 307(a) of the CWA for which EPA has developed section 304(a) criteria guidance. As discussed earlier in this preamble, the section 307(a) list of toxics contains 65 compounds and families of compounds, which potentially include thousands of specific compounds. Of these, the Agency identified a list of 126 ''priority toxic pollutants'' to implement the CWA (see 40 CFR 131.36(b)). Reference in this rule to priority toxic pollutants, toxic pollutants, or toxics refers to the 126 priority toxic pollutants.

EPA has not developed both aquatic life and human health CWA section 304(a) criterion guidance for all of the priority toxic pollutants. The matrix in 40 CFR 131.38(b) contains human health criteria in Column D for 92 priority toxic pollutants which are divided into Column 1: criteria for water consumption (i.e., 2.0 liters per day) and aquatic organism consumption (i.e., 6.5 grams per day of aquatic organisms); and Column 2: criteria for aquatic organism consumption only. The term aquatic organism includes fish and shellfish such as shrimp, clams, oysters and mussels. One reason the total number of priority toxic pollutants with criteria today differs from the total number of priority toxic pollutants contained in earlier published CWA section 304(a) criteria guidance is because EPA has developed and is promulgating chromium criteria for two valence states with respect to aquatic life criteria. Thus, although chromium is a single priority toxic pollutant, there are two criteria for chromium for aquatic life protection. See pollutant 5 in today's rule at 40 CFR 131.38(b). Another reason is that EPA is promulgating human health criteria for nine priority pollutants for which health-based national criteria have been calculated based on information obtained from EPA's IRIS database (EPA provided notice of these nine criteria in the NTR for inclusion in future State triennial reviews. See 57 FR 60848, 60890).

The matrix contains aquatic life criteria for 23 priority pollutants. These are divided into freshwater criteria (Column B) and saltwater criteria (Column C). These columns are further divided into acute and chronic criteria. The aquatic life criteria are considered by EPA to be protective when applied under the conditions described in the section 304(a) criteria documents and in the TSD. For example, water body uses should be protected if the criteria are not exceeded, on average, once every three year period. It should be noted that the criteria maximum concentrations (the acute criteria) are short-term concentrations and that the criteria continuous concentrations (the chronic criteria) are four-day averages. It should also be noted that for certain metals, the actual criteria are equations which are included as footnotes to the matrix. The toxicity of these metals is water hardness dependent and may be adjusted. The values shown in the table are illustrative only, based on a hardness expressed as calcium carbonate of 100 mg/l. Finally, the criterion for pentachlorophenol is pH dependent. The equation is the actual criterion and is included as a footnote. The value shown in the matrix is for a pH of 7.8. Several of the freshwater aquatic life criteria are incorporated into the matrix in the format used in the 1980 criteria methodology which uses a final acute value instead of a continuous maximum concentration. This distinction is noted in footnote g of the table.

The final rule at 40 CFR 131.38(c) establishes the applicability of the criteria to the State of California. 40 CFR 131.38(d) is described later in Section F, of this preamble. EPA has included in this rule provisions necessary to implement numeric criteria in a way that maintains the level of protection intended. These provisions are included in 40 CFR 131.38(c) of today's rule. For example, in order to do steady state waste load allocation analyses, most States have low flow values for streams and rivers which establish flow rates for various purposes. These low flow values become design flows for sizing treatment plants and developing water quality-based effluent limits and/or TMDLs. Historically, these design flows were selected for the purposes of waste load allocation analyses which focused on instream dissolved oxygen concentrations and protection of aquatic life. With the publication of the 1985 TSD, EPA introduced hydrologically and biologically based analyses for the protection of aquatic life and human health. (These concepts have been expanded subsequently in EPA's *Technical Guidance Manual for Performing Wasteload Allocations, Book 6, Design Conditions,* U.S. EPA, 1986. These analyses are included in Appendix D of the revised TSD. The discussion here is greatly simplified and is provided to support EPA's decision to promulgate design flows for instream flows and thereby maintain the adequacy of the criteria for priority toxic pollutants.) EPA recommended either of two methods for calculating acceptable low flows, the traditional hydrologic method developed by the U.S. Geological Survey or a biological based method developed by EPA. Other methods for evaluating the instream flow record may be available; use of these methods may result in TMDLs and/or water quality-based effluent limitations which adequately protect human health and/or aquatic life. The results of either of these two methods, or an equally protective alternative method, may be used.

The State of California may adopt specific design flows for streams and rivers to protect designated uses against the effects of toxics. EPA believes it is

important to specify design flows in today's rule so that, in the absence of state design flows, the criteria promulgated today would be implemented appropriately. The TSD also recommends the use of three dynamic models to perform wasteload allocations. Dynamic wasteload models do not generally use specific steady state design flows but accomplish the same effect by factoring in the probability of occurrence of stream flows based on the historical flow record.

The low flows specified in the rule explicitly contain duration and frequency of occurrence which represent certain probabilities of occurrence. Likewise, the criteria for priority toxic pollutants are defined with duration and frequency components. Dynamic modeling techniques explicitly predict the effects of variability in receiving water, effluent flow, and pollution variation. Dynamic modeling techniques, as described in the TSD, allow for calculating wasteload allocations that meet the criteria for priority toxic pollutants without using a single, worst-case concentration based on a critical condition. Either dynamic modeling or steady state modeling can be used to implement the criteria promulgated today. For simplicity, only steady state conditions are discussed here. Clearly, if the criteria were implemented using design flows that are too high, the resulting toxic controls would not be adequate, because the resulting ambient concentrations would exceed EPA's criteria.

In the case of aquatic life, assuming exceedences occur more frequently than once in three years on the average, exceedences would result in diminished vitality of stream ecosystems characterized by the loss of desired species. Numeric water quality criteria should apply at all flows that are equal to or greater than flows specified below. The low flow values are:

Type of criteria	Design flow
Acute Aquatic Life (CMC).	1 Q 10 or 1 B 3
Chronic Aquatic Life (CCC).	7 Q 10 or 4 B 3
Human Health	harmonic mean flow

Where:

1 Q 10 is the lowest one day flow with an average recurrence frequency of once in 10 years determined hydrologically;

1 B 3 is biologically based and indicates an allowable exceedence of once every 3 years. It is determined by EPA's computerized method (DFLOW model);

7 Q 10 is the lowest average 7 consecutive day low flow with an average recurrence frequency of once in 10 years determined hydrologically;

4 B 3 is biologically based and indicates an allowable exceedences for 4 consecutive days once every 3 years. It is determined by EPA's computerized method (DFLOW model);

EPA is requiring that the harmonic mean flow be applied with human health criteria. The harmonic mean is a standard calculated statistical value. EPA's model for human health effects assumes that such effects occur because of a long-term exposure to low concentration of a toxic pollutant, for example, two liters of water per day for seventy years. To estimate the concentrations of the toxic pollutant in those two liters per day by withdrawal from streams with a high daily variation in flow, EPA believes the harmonic mean flow is the correct statistic to use in computing such design flows rather than other averaging techniques. (For a description of harmonic means see ''Design Stream Flows Based on Harmonic Means,'' Lewis A. Rossman, Jr. of Hydraulics Engineering, Vol. 116, No. 7, July, 1990.)

All waters (including lakes, estuaries, and marine waters), whether or not suitable for such hydrologic calculations, are subject to the criteria promulgated today. Such criteria will need to be attained at the end of the discharge pipe, unless the State authorizes a mixing zone. Where the State plans to authorize a mixing zone, the criteria would apply at the locations allowed by the mixing zone. For example, the chronic criteria (CCC) would apply at the defined boundary of the chronic mixing zone. Discussion of and guidance on these factors are included in the revised TSD in Chapter 4.

EPA is aware that the criteria promulgated today for some of the priority toxic pollutants are at concentrations less than EPA's current analytical detection limits. Analytical detection limits have never been an acceptable basis for setting water quality criteria since they are not related to actual environmental impacts. The environmental impact of a pollutant is based on a scientific determination, not a measuring technique which is subject to change. Setting the criteria at levels that reflect adequate protection tends to be a forcing mechanism to improve analytical detection methods. See 1985 Guidelines, page 21. As the methods improve, limits based on the actual criteria necessary to protect aquatic life and human health become measurable. The Agency does not believe it is appropriate to promulgate criteria that are not sufficiently protective. EPA discusses this issue further in its Response to Comment Document for today's final rule.

EPA does believe, however, that the use of analytical detection limits are appropriate for assessing *compliance* with National Pollutant Discharge Elimination System (NPDES) permit limits. This view of the role of detection limits was first articulated in guidance for translating dioxin criteria into NPDES permit limits. See ''Strategy for the Regulation of Discharges of PHDDs and PHDFs from Pulp and Paper Mills to Waters of the U.S.'' Memorandum from the Assistant Administrator for Water to the Regional Water Management Division Directors, May 21, 1990. This guidance presented a model for addressing toxic pollutants which have criteria less than current detection limits. EPA, in more recent guidance, recommends the use of the ''minimum level'' or ML for reporting sample results to assess compliance with WQBELs (TSD page 111). The ML, also called the ''quantification level,'' is the level at which the entire analytical system gives recognizable mass spectra and acceptable calibration points, i.e., the point at which the method can reliably quantify the amount of pollutant in the sample. States can use their own procedures to average and otherwise account for monitoring data, *e.g.,* quantifying results below the ML. These results can then be used to assess compliance with WQBELs. (See 40 CFR part 132, Appendix F, Procedure 8.B.) This approach is applicable to priority toxic pollutants with criteria less than current detection limits. EPA's guidance explains that standard analytical methods may be used for purposes of assessing compliance with permit limits, but not for purposes of establishing water quality criteria or permit limits. Under the CWA, analytical methods are appropriately used in connection with NPDES permit limit compliance assessments. Because of the function of water quality criteria, EPA has not considered the sensitivity of analytical methods in deriving the criteria promulgated today.

EPA has promulgated 40 CFR 131.38(c)(3) to determine when freshwater or saltwater aquatic life criteria apply. This provision incorporates a time parameter to better define the critical condition. The structure of the paragraph is to establish

applicable rules and to allow for site-specific exceptions where the rules are not consistent with actual field conditions. Because a distinct separation generally does not exist between freshwater and saltwater aquatic communities, EPA is establishing the following: (1) The freshwater criteria apply at salinities of 1 part per thousand and below at locations where this occurs 95% or more of the time; (2) saltwater criteria apply at salinities of 10 parts per thousand and above at locations where this occurs 95% more of the time; and (3) at salinities between 1 and 10 parts per thousand the more stringent of the two apply unless EPA approves the application of the freshwater or saltwater criteria based on an appropriate biological assessment. The percentiles included here were selected to minimize the chance of overlap, that is, one site meeting both criteria. Determination of these percentiles can be done by any reasonable means such as interpolation between points with measured data or by the application of calibrated and verified mathematical models (or hydraulic models). It is not EPA's intent to require actual data collection at particular locations.

In the brackish water transition zones of estuaries with varying salinities, there generally will be a mix of freshwater and saltwater species. Generally, therefore, it is reasonable for the more stringent of the freshwater or saltwater criteria to apply. In evaluating appropriate data supporting the alternative set of criteria, EPA will focus on the species composition as its preferred method. This assignment of criteria for fresh, brackish and salt waters was developed in consultation with EPA's research laboratories at Duluth, Minnesota and Narragansett, Rhode Island. The Agency believes such an approach is consistent with field experience.

Paragraph (d) in 40 CFR 131.38 lists the designated water and use classifications for which the criteria apply. The criteria are applied to the beneficial use designations adopted by the State of California; EPA has not promulgated any new use classifications in this rule.

Exceedences Frequency: In a water quality criterion for aquatic life, EPA recommends an allowable frequency for excursions of the criteria. See 1985 Guidelines, pages 11–13. This allowable frequency provides an appropriate period of time during which the aquatic community can recover from the effect of an excursion and then function normally for a period of time before the next excursion. An excursion is defined as an occurrence of when the average concentration over the duration of the averaging period is above the CCC or the CMC. As ecological communities are naturally subjected to a series of stresses, the allowable frequency of pollutant stress may be set at a value that does not significantly increase the frequency or severity of all stresses combined. See also TSD, Appendix D. In addition, providing an allowable frequency for exceeding the criterion recognizes that it is not generally possible to assure that criteria are never exceeded. (TSD, page 36.)

Based on the available data, today's rule requires that the acute criterion for a pollutant be exceeded no more than once in three years on the average. EPA is also requiring that the chronic criterion for a pollutant be exceeded no more than once in three years on the average. EPA acknowledges that States may develop allowable frequencies that differ from these allowable frequencies, so long as they are scientifically supportable, but believes that these allowable frequencies are protective of the designated uses where EPA is promulgating criteria.

The use of aquatic life criteria for developing water quality-based effluent limits in permits requires the permitting official to use an appropriate wasteload allocation model. (TSD, Appendix D–6.) As discussed above, there are generally two methods for determining design flows, the hydrologically-based method and the biologically-based method.

The biologically-based method directly uses the averaging periods and frequencies specified in the aquatic life criteria for determining design flows. (TSD, Appendix. D–8.) Because the biologically-based method calculates the design flow directly from the duration and allowable frequency, it most accurately provides the allowed number of excursions. The hydrologically based method applies the CMC at a design flow equal to or equivalent to the 1Q10 design flow (i.e., the lowest one-day flow with an average recurrence frequency of once in ten years), and applies the CCC at the 7Q10 design flow (i.e., the lowest average seven consecutive day flow with a recurrence frequency of once in ten years).

EPA established a three year allowable frequency in the NTR. In settlement of the litigation on the NTR, EPA stated that it was in the midst of conducting, sponsoring, or planning research aimed at addressing scientific issues related to the basis for and application of water quality criteria and mentioned the issue of allowable frequency. See Partial Settlement Agreement in *American Forest and Paper Ass'n, Inc. et al.* v. *U.S. EPA* (Consolidated Case No. 93–0694 (RMU) D.D.C. To that end, EPA is reevaluating issues raised about allowable frequency as part of its work in revising the 1985 Guidelines.

EPA recognizes that additional data concerning (a) the probable frequency of lethal events for an assemblage of taxa covering a range of sensitivities to pollutants, (b) the probable frequency of sublethal effects for such taxa, (c) the differing effects of lethal and sublethal events in reducing populations of such taxa, and (d) the time needed to replace organisms lost as a result of toxicity, may lead to further refinement of the allowable frequency value. EPA has not yet completed this work. Until this work is complete, EPA believes that where EPA promulgates criteria, the three year allowable frequency represents a value in the reasonable range for this parameter.

3. Implementation

Once the applicable designated uses and water quality criteria for a water body are determined, under the National Pollutant Discharge Elimination System (NPDES) program discharges to the water body must be characterized and the permitting authority must determine the need for permit limits. If a discharge causes, has the reasonable potential to cause, or contributes to an excursion of a numeric or narrative water quality criteria, the permitting authority must develop permit limits as necessary to meet water quality standards. These permit limits are water quality-based effluent limitations or WQBELs. The terms ''cause,'' ''reasonable potential to cause,'' and ''contribute to'' are the terms in the NPDES regulations for conditions under which water quality-based permit limits are required. See 40 CFR 122.44(d)(1).

Since the publication of the proposed CTR, the State of California adopted procedures which detail how water quality criteria will be implemented through NPDES permits, waste discharge requirements, and other regulatory approaches. These procedures entitled, *Policy for Implementation of Toxics Standards for Inland Surface Waters, Enclosed Bays, and Estuaries of California* were adopted on March 2, 2000. Once these procedures are submitted for review under CWA section 303(c), EPA will review them as they relate to water quality standards, and approve or disapprove them.

Several commenters understood the language in the preamble to the proposed rule regarding implementation

to mean that site-specific criteria, variances, and other actions would be prohibited or severely limited by the CTR. Site-specific criteria, variances and other actions modifying criteria are neither prohibited nor limited by the CTR. The State, if it so chooses, still can make these changes to its water quality standards, subject to EPA approval. However, with this Federal rule in effect, the State cannot implement any modifications that are less stringent than the CTR without an amendment to the CTR to reflect these modifications. EPA will make every effort to expeditiously accommodate Federal rulemaking of appropriate modifications to California's water quality standards. In the preamble to the proposed CTR, and here today, EPA is emphasizing that these efforts to amend the CTR on a case-by-case basis will generally increase the time before a modification can be implemented.

4. Wet Weather Flows

EPA has for a longtime maintained that CWA section 301(b)(1)(C) applies to NPDES permits for discharges from municipal separate storm sewer systems. Recently, the U.S. Court of Appeals for the Ninth Circuit upheld NPDES permits issued by EPA for five Arizona municipal separate storm sewer systems and addressed this issue specifically. *Defenders of Wildlife, et al.* v. *Browner,* No. 98–71080 (9th Cir., October 1999). The Court held that the CWA does not require ''strict compliance'' with State water quality standards for municipal storm sewer permits under section 301(b)(1)(C), but that at the same time, the CWA does give EPA discretion to incorporate appropriate water quality-based effluent limitations under another provision, CWA section 402(p)(3)(B)(iii).

The Court based its decision on the structure of section 402(p)(3), which contains distinct language for discharges of industrial storm water and municipal storm water. In section 402(p)(3)(A), Congress requires that ''dischargers associated with industrial activity shall meet all applicable provisions of [section 402] and section [301].'' 33 U.S.C. section 1342(p)(3)(A). The Court noted, therefore, that by incorporation, industrial storm water discharges need to achieve ''any more stringent limitation, including those necessary to meet water quality standards * * *'' The Court explained that industrial storm water discharges ''must comply strictly with State water quality standards'' but that Congress chose not to include a similar provision for municipal storm sewer discharges, including instead a requirement for controls to reduce pollutants to the maximum extent practicable or MEP standard in section 402(p)(3)(B). Reading the two related sections together, the Court concluded that section 402(p)(3)(B)(iii) does not require ''strict compliance'' by municipal storm sewer discharges according to section 301(b)(1)(C). At the same time, however, the Court found that the language in CWA section 402(p)(3)(B)(iii) which states that permits for discharges from municipal storm sewers shall require ''such other provisions as the Administrator of the state determines appropriate for the control of such pollutants'' provides EPA with discretion to incorporate provisions lending to ultimate compliance with water quality standards.

EPA believes that compliance with water quality standards through the use of Best Management Practices (BMPs) is appropriate. EPA articulated its position on the use of BMPs in storm water permits in the policy memorandum entitled, ''Interim Permitting Approach for Water Quality-Based Effluent Limitations In Storm Water Permits'' which was signed by the Assistant Administrator for Water, Robert Perciasepe on August 1, 1996 (61 FR 43761, August 9, 1996). A copy of this memorandum is contained in the administrative record for today's rule. The policy affirms the use of BMPs as a means to attain water quality standards in municipal storm water permits, and embraces BMPs as an interim permitting approach.

The interim permitting approach uses BMPs in first-round storm water permits, and expanded or better-tailored BMPs in subsequent permits, where necessary, to provide for the attainment of water quality standards. In cases where adequate information exists to develop more specific conditions or limitations to meet water quality standards, these conditions or limitations are to be incorporated into storm water permits, as necessary and appropriate.

This interim permitting approach, however, only applies to EPA. EPA encourages the State to adopt a similar policy for municipal storm water permits. This interim permitting approach provides time, where necessary, to more fully assess the range of issues and possible options for the control of storm water discharges for the protection of water quality. More information on this issue is included in the response to comment document in response to specific storm water issues raised by commenters.

5. Schedules of Compliance

A compliance schedule refers to an enforceable sequence of interim requirements in a permit leading to ultimate compliance with water quality-based effluent limitations or WQBELs in accordance with the CWA. The authorizing compliance schedule provision authorizes, but does not require, the permit issuing authority in the State of California to include such compliance schedules in permits under appropriate circumstances. The State of California is authorized to administer the National Pollutant Discharge Elimination System (NPDES) program and may exercise its discretion when deciding if a compliance schedule is justified because of the technical or financial (or other) infeasibility of immediate compliance. An authorizing compliance schedule provision is included in today's rule because of the potential for existing dischargers to have new or more stringent effluent limitations for which immediate compliance would not be possible or practicable.

New and Existing Dischargers: The provision allows compliance schedules only for an ''existing discharger'' which is defined as any discharger which is not a ''new California discharger.'' A ''new California discharger'' includes ''any building, structure, facility, or installation from which there is, or may be, a 'discharge of pollutants', the construction of which commences after the effective date of this regulation.'' These definitions are modeled after the existing 40 CFR 122.2 definitions for parallel terms, but with a cut-off date modified to reflect this rule. Only ''new California dischargers'' are required to comply immediately upon commencement of discharge with effluent limitations derived from the criteria in this rule. For ''existing dischargers'' whose permits are reissued or modified to contain new or more stringent limitations based upon certain water quality requirements, the permit could allow up to five years, or up to the length of a permit, to comply with such limitations. The provision applies to new or more stringent effluent limitations based on the criteria in this EPA rule.

EPA has included ''increasing dischargers'' within the category of ''existing dischargers'' since ''increasing dischargers'' are existing facilities with a change—an increase—in their discharge. Such facilities may include those with seasonal variations. ''Increasing dischargers'' will already have treatment systems in place for their current discharge, thus, they have less

opportunity than a new discharger does to design and build a new treatment system which will meet new water quality-based requirements for their changed discharge. Allowing existing facilities with an increasing discharge a compliance schedule will avoid placing the discharger at a competitive disadvantage vis-a-vis other existing dischargers who are eligible for compliance schedules.

Today's rule does not prohibit the use of a short-term ''shake down period'' for new California dischargers as is provided for new sources or new dischargers in 40 CFR 122.29(d)(4). These regulations require that the owner or operator of (1) a new source; (2) a new discharger (as defined in 40 CFR 122.2) which commenced discharge after August 13, 1979; or (3) a recommencing discharger shall install and implement all pollution control equipment to meet the conditions of the permit before discharging. The facility must also meet all permit conditions in the shortest feasible time (not to exceed 90 days). This shake-down period is not a compliance schedule. This approach may be used to address violations which may occur during a new facility's start-up, especially where permit limits are water quality-based and biological treatment is involved.

The burden of proof to show the necessity of a compliance schedule is on the discharger, and the discharger must request approval from the permit issuing authority for a schedule of compliance. The discharger should submit a description of the minimum required actions or evaluations that must be undertaken in order to comply with the new or more restrictive discharge limits. Dates of completion for the required actions or evaluations should be included, and the proposed schedule should reflect the shortest practicable time to complete all minimum required actions.

Duration of Compliance Schedules: Today's rule provides that compliance schedules may provide for up to five years to meet new or more stringent effluent limitations in those limited circumstances where the permittee can demonstrate to the permit authority that an extended schedule is warranted. EPA's regulations at 122.47 require compliance with standards as soon as possible. This means that permit authorities should not allow compliance schedules where the permittee fails to demonstrate their necessity. This provision should not be considered a default compliance schedule duration for existing facilities.

In instances where dischargers wish to conduct toxicological studies, analyze results, and adopt and implement new or revised water quality-based effluent limitations, EPA believes that five years is sufficient time within which to complete this process. See the preamble to the proposed rule.

Under this rule, where a schedule of compliance exceeds one year, interim requirements are to be specified and interim progress reports are to be submitted at least annually to the permit issuing authority, in at least one-year time intervals.

The rule allows all compliance schedules to extend up to a maximum duration of five years, which is the maximum term of any NPDES permit. See 40 CFR 122.46. The discharger's opportunity to obtain a compliance schedule occurs when the existing permit for that discharge is issued, reissued or modified to contain more stringent limits based on the water quality criteria in today's rule. Such compliance schedules, however, cannot be extended to any indefinite point of time in the future because the compliance schedule provision in this rule will sunset on May 18, 2005. The sunset applies to the authorizing provision in today's rule (40 CFR 131.38(e)), not to individual schedules of compliance included in specific NPDES permits. Delays in reissuing expired permits (including those which continue in effect under applicable NPDES regulations) cannot indefinitely extend the period of time during which a compliance schedule is in effect. This would occur where the permit authority includes the single maximum five-year compliance schedule in a permit that is reissued just before the compliance schedule provision sunsets (having been previously issued without WQBELS using the rule's criteria on the eve of the effective date of this rule). Instead, the effect of the sunset provision is to limit the longest time period for compliance to ten years after the effective date of this rule.

EPA recognizes that where a permit is modified during the permit term, and the permittee needs the full five years to comply, the five-year schedule may extend beyond the term of the modified permit. In such cases, the rule allows for the modified permit to contain a compliance schedule with an interim limit by the end of the permit term. When the permit is reissued, the permit authority may extend the compliance schedule in the next permit, provided that, taking into account the amount of time allowed under the previous permit, the entire compliance schedule contained in the permit shall not exceed five years. Final permit limits and compliance dates will be included in the record for the permit. Final compliance dates must occur within five years from the date of permit issuance, reissuance, or modification, unless additional or less time is provided for by law.

EPA would prefer that the State adopt an authorizing compliance schedule provision but recognizes that the State may not be able to complete this action for some time after promulgation of the CTR. Thus, EPA has chosen to promulgate the rule with a sunset provision which states that the authorizing compliance schedule provision will cease or sunset on May 18, 2005. However, if the State Board adopts, and EPA approves, a statewide authorizing compliance schedule provision significantly prior to May 18, 2005, EPA will act to stay the authorizing compliance schedule provision in today's rule. Additionally, if a Regional Board adopts, and the State Board adopts and EPA approves, a Regional Board authorizing compliance schedule provision, EPA will act to stay today's provision for the appropriate or corresponding geographic region in California. At that time, the State Board's or Regional Board's authorizing compliance schedule provision will govern the ability of the State regulatory entity to allow a discharger to include a compliance schedule in a discharger's NPDES permit.

Antibacksliding: EPA wishes to address the potential concern over antibacksliding where revised permit limits based on new information are the result of the completion of additional studies. The Agency's interpretation of the CWA is that the antibacksliding requirements of section 402(o) of the CWA do not apply to revisions to effluent limitations made before the scheduled date of compliance for those limitations.

State Compliance Schedule Provisions: EPA supports the State in adopting a statewide provision independent of or as part of the effort to readopt statewide water quality control plans, or in adopting individual basin-wide compliance schedule provisions through its nine Regional Water Quality Control Boards (RWQCBs). The State and RWQCBs have broad discretion to adopt a provision, including discretion on reasonable lengths of time for final compliance with WQBELs. EPA recognizes that practical time frames within which to set interim goals may be necessary to achieve meaningful, long-term improvements in water quality in California.

At this time, two RWQCBs have adopted an authorizing compliance schedule provision as an amendment to

their respective Basin Plans during the Boards' last triennial review process. The Basin Plans have been adopted by the State and have come to EPA for approval. Thus, the Basin Plans' provisions are effective for the respective Basins. If and when EPA approves of either Regional Basin Plan, EPA will expeditiously act to amend the CTR, staying its compliance schedule provision, for the appropriate geographic region.

6. Changes From Proposed Rule

A few changes were made in the final rule from the proposal both as a result of the Agency's consideration of issues raised in public comments and Endangered Species Act consultation with the U.S. Fish and Wildlife Service (FWS) and U.S. National Marine Fisheries Service (NMFS). The important changes include: reserving the mercury aquatic life criteria; reserving the selenium freshwater acute aquatic life criterion; reserving the chloroform human health criteria; and adding a sunset provision to the authorizing compliance schedule provision. EPA also clarified that the CTR will not replace priority toxic pollutant criteria which were adopted by the San Francisco Regional Water Quality Control Board in its 1986 Basin Plan, adopted by the State Board, and approved by EPA; specifying the harmonic mean for human health criteria for non-carcinogens and adding a provision which explicitly allows the State to adopt and implement an alternative averaging period, frequency, and design flow for a criterion after opportunity for public comment.

The first two changes, the reservation of mercury criteria and selenium criterion, are discussed in more detail below in Section L., The Endangered Species Act (ESA). The selenium criterion is also discussed in more detail above in Section E., Derivation of Criteria, in subsection 2.b., Freshwater Acute Selenium Criterion. EPA has also decided to reserve a decision on numeric criteria for chloroform and therefore not promulgate chloroform criteria in the final rule. As part of a large-scale regulation promulgated in December l998 under the Safe Drinking Water Act, EPA published a health-based goal for chloroform (the maximum contaminant level goal or MCLG) of zero, see 63 FR 69390, Dec. 16, 1998. EPA provided new data and analyses concerning chloroform for public review and comment, including a different, mode of action approach for estimating the cancer risk, 63 FR 15674, March 31, 1998, but did not reach a conclusion on how to use that new information in establishing the final MCLG, pending further review by the Science Advisory Board. EPA has now concluded that any further actions on water quality criteria should take into account the new data and analysis as reviewed by the SAB. This decision is consistent with a recent federal court decision vacating the MCLG for chloroform (*Chlorine Chemistry Council* v. *EPA,* No. 98–1627 (DC Cir., Mar. 31,2000)). EPA intends to reassess the human health 304(a) criteria recommendation for chloroform. For these reasons, EPA has decided to reserve a decision on numeric criteria for chloroform in the CTR and not promulgate water quality criteria as proposed. Permitting authorities in California should continue to rely on existing narrative criteria to establish effluent limitations as necessary for chloroform.

The sunset provision for the authorizing compliance schedule provision has been added to ease the transition from a Federal provision to the State's provision that was adopted in March 2000 as part of its' new statewide implementation plan. The sunset provision is discussed in more detail in Section G.5 of today's preamble. The CTR matrix at 40 CFR 131.38(b)(1) makes it explicit that the rule does not supplant priority toxic pollutant criteria which were adopted by the San Francisco Regional Water Quality Control Board in its 1986 Basin Plan, adopted by the State Board, and approved by EPA. This change is discussed more fully in Section D.4. of today's preamble. EPA modified the design flow for implementing human health criteria for non-carcinogens from a 30Q5 to a harmonic mean. Human health criteria for non-carcinogens are based on an RfD, which is an acceptable daily exposure over a lifetime. EPA matched the criteria for protection over a human lifetime with the longest stream flow averaging period, i.e., the harmonic mean. Lastly, the CTR now contains language which is intended to make it easier for the State to adopt and implement an alternative averaging period, frequency and related design flow, for situations where the default parameters are inappropriate. This language is found at 40 CFR 131.38(c)(2)(iv).

H. Economic Analysis

This final rule establishes ambient water quality criteria which, by themselves, do not directly impose economic impacts (see section K). These criteria combined with the State-adopted designated uses for inland surface waters, enclosed bays and estuaries, and implementation policies, will establish water quality standards. Until the State implements these water quality standards, there will be no effect of this rule on any entity. The State will implement these criteria by ensuring that NPDES permits result in discharges that will meet these criteria. In so doing, the State will have considerable discretion.

EPA has analyzed the indirect potential costs and benefits of this rule. In order to estimate the indirect costs and benefits of the rule, an appropriate baseline must be established. The baseline is the starting point for measuring incremental costs and benefits of a regulation. The baseline is established by assessing what would occur in the absence of the regulation. At present, State Basin Plans contain a narrative water quality criterion stating that all waters shall be maintained free of toxic substances in concentrations that produce detrimental physiological responses in human, plant, animal, or aquatic life. EPA's regulation at 40 CFR 122.44(d)(1)(vi) requires that where a discharge causes or has the reasonable potential to cause an excursion above a narrative criterion within a State water quality standard, the permitting authority must establish effluent limits but may determine limits using a number of options. These options include establishing ''effluent limits on a case-by-case basis, using EPA's water quality criteria published under section 304(a) of the CWA, supplemented where necessary by other relevant information'' (40 CFR 122.44(d)(1)(vi)(B)). Thus, to the extent that the State is implementing its narrative criteria by applying the CWA section 304(a) criteria, this rule does not impose any incremental costs because the criteria in this rule are identical to the CWA section 304(a) criteria. Alternatively, to the extent that the State is implementing its narrative criteria on a ''case-by-case basis'' using ''other relevant information'' in its permits this rule may impose incremental indirect costs because the criteria in these permits may not be based on CWA 304(a) criteria. Both of these approaches to establishing effluent limits are in full compliance with the CWA.

Because a specific basis for effluent limits in all existing permits in California is not known, it is not possible to determine a precise estimate of the indirect costs of this rule. The incremental costs of the rule may be as low as zero, or as high as $61 million. The high estimate of costs is based on the possibility that most of the effluent limits now in effect are not based on 304(a) criteria. EPA evaluated these

indirect costs using two different approaches. The first approach uses existing discharge data and makes assumptions about future State NPDES permit limits. Actual discharge levels are usually lower than the level set by current NPDES permit limits. This approach, representing the low-end scenario, also assumes that some of the discretionary mechanisms that would enhance flexibility (*e.g.,* site specific criteria, mixing zones) would be granted by the State. The second approach uses a sample of existing permit limits and assumes that dischargers are actually discharging at the levels contained in their permits and makes assumptions about limits statewide that would be required under the rule. This approach, representing the high-end scenario, also assumes that none of the discretionary mechanisms that would enhance flexibility (*e.g.,* site specific criteria, mixing zones) would be granted by the State. These two approaches recognize that the State has significant flexibility and discretion in how it chooses to implement standards within the NPDES permit program, the EA by necessity includes many assumptions about how the State will implement the water quality standards. These assumptions are based on a combination of EPA guidance and current permit conditions for the facilities examined in this analysis. To account for the uncertainty of EPA's implementation assumptions, this analysis estimates a wide range of costs and benefits. By completing the EA, EPA intends to inform the public about how entities might be potentially affected by State implementation of water quality standards in the NPDES permit program. The costs and benefits sections that follow summarize the methodology and results of the analysis.

1. Costs

EPA assessed the potential compliance costs that facilities may incur to meet permit limits based on the criteria in today's rule. The analysis focused on direct compliance costs such as capital costs and operation and maintenance costs (O&M) for end-of-pipe pollution control, indirect source controls, pollution prevention, monitoring, and costs of pursuing alternative methods of compliance.

The population of facilities with NPDES permits that discharge into California's enclosed bays, estuaries and inland surface waters includes 184 major dischargers and 1,057 minor dischargers. Of the 184 major facilities, 128 are publicly owned treatment works (POTWs) and 56 are industrial facilities. Approximately 2,144 indirect dischargers designated as significant industrial users discharge wastewater to those POTWs. In the EA for the proposed CTR, EPA used a three-phased process to select a sample of facilities to represent California dischargers potentially affected by the State's implementation of permit limits based on the criteria contained in this rule.

The first phase consisted of choosing three case study areas for which data was thought to exist. The three case studies with a total of 5 facilities included: the South San Francisco Bay (the San Jose/Santa Clara Water Pollution Control Plant and Sunnyvale Water Pollution Control Plant); the Sacramento River (the Sacramento Regional Wastewater Treatment Plant); and the Santa Ana River (the City of Riverside Water Quality Control Plant and the City of Colton Municipal Wastewater Treatment Facility). The second phase consisted of selecting five additional major industrial dischargers to complement the case-study POTWs.

The third phase involved selecting 10 additional facilities to improve the basis for extrapolating the costs of the selected sample facilities to the entire population of potentially affected dischargers. The additional 10 facilities were selected such that the group examined: (1) Was divided between major POTWs and major industrial discharger categories in proportion to the numbers of facilities in the State; (2) gave greater proportionate representation to major facilities than minor facilities based on a presumption that the majority of compliance costs would be incurred by major facilities; (3) gave a proportionate representation to each of four principal conventional treatment processes typically used by facilities in specified industries in California; and (4) was representative of the proportionate facilities located within the different California Regional Water Quality Control Boards. Within these constraints, facilities were selected at random to complete the sample.

In the EA for today's final rule, EPA primarily used the same sample as the EA for the proposed rule with some modifications. EPA increased the number of minor POTWs and minor industrial facilities in the sample. EPA randomly selected four new minor POTW facilities and five new minor industrial facilities to add to the sample. The number of sample facilities selected in each area under the jurisdiction of a Regional Water Quality Control Board was roughly proportional to the universe of facilities in each area.

For those facilities that were projected to exceed permit limits based on the criteria, EPA estimated the incremental costs of compliance. Using a decision matrix or flow chart, costs were developed for two different scenarios—a ''low-end'' cost scenario and a ''high-end'' cost scenario—to account for a range of regulatory flexibility available to the State when implementing permit limits based on the water quality criteria. The assumptions for baseline loadings also vary over the two scenarios. The low-end scenario generally assumed that facilities were discharging at the maximum effluent concentrations taken from actual monitoring data, while the high-end scenario generally assumed that facilities were discharging at their current effluent limits. The decision matrix specified assumptions used for selection of control options, such as optimization of existing treatment processes and operations, in-plant pollutant minimization and prevention, and end-of-pipe treatment.

The annualized potential costs that direct and indirect dischargers may incur as a result of State implementation of permit limits based on water quality standards using today's criteria are estimated to be between $33.5 million and $61 million. EPA believes that the costs incurred as a result of State implementation of these permit limits will approach the low-end of the cost range. Costs are unlikely to reach the high-end of the range because State authorities are likely to choose implementation options that provide some degree of flexibility or relief to point source dischargers. Furthermore, cost estimates for both scenarios, but especially for the high-end scenario, may be overstated because the analysis tended to use conservative assumptions in calculating these permit limits and in establishing baseline loadings. The baseline loadings for the high-end were based on current effluent limits rather than actual pollutant discharge data. Most facilities discharge pollutants in concentrations well below current effluent limits. In addition, both the high-end and low-end cost estimates in the EA may be slightly overstated since potential costs incurred to reduce chloroform discharges were included in these estimates. EPA made a decision to reserve the chloroform human health criteria after the EA was completed.

Under the low-end cost scenario, major industrial facilities and POTWs would incur about 27 percent of the potential costs, indirect dischargers would incur about 70 percent of the potential costs, while minor dischargers would incur about 3 percent. Of the major direct dischargers, POTWs would incur the largest share of projected costs (87 percent). However, distributed

among 128 major POTWs in the State, the average cost per plant would be $61,000 per year. Chemical and petroleum industries would incur the highest cost of the industrial categories (5.6 percent of the annual costs, with an annual average of $25,200 per plant). About 57 percent of the low-end costs would be associated with pollution prevention activities, while nearly 38 percent would be associated with pursuing alternative methods of compliance under the regulations.

Under the high-end cost scenario, major industrial facilities and POTWs would incur about 94 percent of the potential costs, indirect dischargers would incur about 17 percent of the potential costs, while minor dischargers would incur about 5 percent. Among the major, direct dischargers, two categories would incur the majority of potential costs—major POTWs (82 percent), Chemical/Petroleum Products (9 percent). The average annual per plant cost for different industry categories would ranges from zero to $324,000. The two highest average cost categories would be major POTWs ($324,000 per year) and Chemical/Petroleum Products ($221,264 per year). The shift in proportion of potential costs between direct and indirect dischargers is due to the assumption that more direct dischargers would use end-of-pipe treatment under the high-end scenario. Thus, a smaller proportion of indirect dischargers would be impacted under the high-end scenario, since some municipalities are projected to add end-of-pipe treatment which would reduce the need for controls from indirect discharges. Over 91 percent of the annual costs are for waste minimization and treatment optimization costs. Waste minimization would represent nearly 84% of the total annual costs. Capital and operation and maintenance costs would make up less than 9 percent of annual costs.

Cost-Effectiveness: Cost-effectiveness is estimated in terms of the cost of reducing the loadings of toxic pollutants from point sources. The cost-effectiveness is derived by dividing the projected annual costs of implementing permit limits based on water quality standards using today's criteria by the toxicity-weighted pounds (pound-equivalents) of pollutants removed. Pound-equivalents are calculated by multiplying pounds of each pollutant removed by the toxic weight (based on the toxicity of copper) for that pollutant.

Based on this analysis, State implementation of permit limits based on today's criteria would be responsible for the reduction of about 1.1 million to 2.7 million toxic pound-equivalents per year, or 15 to 50 percent of the toxic-weighted baseline loadings for the high- and low-end scenarios, respectively. The cost-effectiveness of the scenarios would range from $22 (high-end scenario) to $31 (low-end scenario) per pound-equivalent.

2. Benefits

The benefits analysis is intended to provide insight into both the types and potential magnitude of the economic benefits expected as a result of implementation of water quality standards based on today's criteria. To the extent feasible, empirical estimates of the potential magnitude of the benefits were developed and then compared to the estimated costs of implementing water quality standards based on today's criteria.

To perform a benefits analysis, the types or categories of benefits that apply need to be defined. EPA relied on a set of benefits categories that typically apply to changes in the water resource environment. Benefits were categorized as either use benefits or passive (nonuse) benefits depending on whether or not they involve direct use of, or contact with, the resource. The most prominent use benefit categories are those related to recreational fishing, boating, and swimming. Another use benefit category of significance is human health risk reduction. Human health risk reductions can be realized through actions that reduce human exposure to contaminants such as exposure through the consumption of fish containing elevated levels of pollutants. Passive use benefits are those improvements in environmental quality that are valued by individuals apart from any use of the resource in question.

Benefits estimates were derived in this study using an approach in which benefits of discrete large-scale changes in water quality beyond present day conditions were estimated wherever feasible. A share of those benefits was then apportioned to implementation of water quality standards based on today's criteria. The apportionment estimate was based on a three-stage process:

First, EPA assessed current total loadings from all sources that are contributing to the toxics-related water quality problems observed in the State. This defines the overall magnitude of loadings. Second, the share of total loadings that are attributable to sources that would be controlled through implementation of water quality standards based on today's criteria was estimated. Since this analysis was designed to focus only on those controls imposed on point sources, this stage of the process entailed estimating the portion of total loadings originating from point sources. Third, the percentage reduction in loadings expected due to implementation of today's criteria was estimated and then multiplied by the share of point source loadings to calculate the portion of benefits that could be attributed to implementation of water quality standards based on today's criteria.

Total monetized annual benefits were estimated in the range of $6.9 to $74.7 million. By category, annual benefits would be $1.3 to $4.6 million for avoided cancer risk, $2.2 to $15.2 million for recreational angling, and $3.4 to $54.9 million for passive use benefits.

There are numerous categories of potential or likely benefits that have been omitted from the quantified and monetized benefit estimates. In terms of potential magnitudes of benefit, the following are likely to be significant contributors to the underestimation of the monetized values presented above:

- Improvements in water-related (in-stream and near stream) recreation apart from fishing. The omission of potential motorized and nonmotorized boating, swimming, picnicking, and related in-stream and stream-side recreational activities from the benefits estimates could contribute to an appreciable underestimation of total benefits. Such recreational activities have been shown in empirical research to be highly valued, and even modest changes in participation and or user values could lead to sizable benefits statewide. Some of these activities can be closely associated with water quality attributes (notably, swimming). Other recreational activities may be less directly related to the water quality improvements, but might nonetheless increase due to their association with fishing, swimming, or other activities in which the participants might engage.
- Improvements in consumptive and nonconsumptive land-based recreation, such as hunting and wildlife observation. Improvements in aquatic habitats may lead (via food chain and related ecologic benefit mechanisms) to healthier, larger, and more diverse populations of avian and terrestrial species, such as waterfowl, eagles, and otters. Improvements in the populations for these species could manifest as improved hunting and wildlife viewing opportunities, which might in turn increase participation and user day values for such activities. Although the scope of the benefits analysis has not allowed a quantitative assessment of these values at either pre- or post-rule

conditions, it is conceivable that these benefits could be appreciable.

• Improvements in human health resulting from reduction of non-cancer risk. EPA estimated that implementation of water quality standards based on the criteria would result in a reduction of mercury concentrations in fish tissue and, thus, a reduction in the hazard from consumption of mercury contaminated fish. However, EPA was unable to monetize benefits due to reduced non-cancer health effects.

• Human health benefits for saltwater anglers outside of San Francisco Bay were not estimated. The number of saltwater anglers outside of San Francisco Bay is estimated to be 673,000 (based on Huppert, 1989, and U.S. FWS, 1993). The omission of other saltwater anglers may cause human health benefits to be underestimated. In addition, benefit estimates in the EA may be slightly overstated since potential benefits from reductions in chloroform discharges were included in these estimates. EPA made a decision to reserve the chloroform human health criteria after the EA was completed.

EPA received a number of comments which requested the Agency use the cost-benefit analysis in the EA as a factor in setting water quality criteria. EPA does not use the EA as a basis in determining protective water quality criteria. EPA's current regulations at 40 CFR 131.11 state that the criteria must be based on sound scientific rationale and must protect the designated use. From the outset of the water quality standards program, EPA has explained that while economic factors may be considered in designating uses, they may not be used to justify criteria that are not protective of those uses. 44 FR 25223–226, April 30, 1979. See e.g. *Mississippi Commission on Natural Resources* v. *Costle,* 625 F. 2d 1269, 1277 (5th Cir. 1980). EPA reiterated this interpretation of the CWA and its implementing regulations in discussing section 304(a) recommended criteria guidance stating that ''they are based solely on data and scientific judgments on the relationship between pollutant concentrations and environmental and human health effects and do not reflect consideration of economic impacts or the technological feasibility of meeting the chemical concentrations in ambient water.'' 63 FR 36742 and 36762, July 7, 1998.

I. Executive Order 12866, Regulatory Planning and Review

Under Executive Order 12866 (58 FR 51735, October 4, 1993), the Agency must determine whether the regulatory action is ''significant'' and therefore subject to Office of Management and Budget (OMB) review and the requirements of the Executive Order. The Order defines ''significant regulatory action'' as one that is likely to result in a rule that may:

(1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities;

(2) Create a serious inconsistency or otherwise interfere with an action taken or planned by another Agency;

(3) Materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or

(4) Raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order.

It has been determined that this rule is not a ''significant regulatory action'' under the terms of Executive Order 12866 and is therefore not subject to OMB review.

J. Unfunded Mandates Reform Act of 1995

Title II of the Unfunded Mandates Reform Act of 1995 (UMRA), Public Law 104–4, establishes requirements for Federal agencies to assess the effects of their regulatory actions on State, local, and tribal governments and the private sector. Under section 202 of the UMRA, EPA generally must prepare a written statement, including a cost-benefit analysis, for proposed and final rules with ''Federal mandates'' that may result in expenditures to State, local, and tribal governments, in the aggregate, or to the private sector, of $100 million or more in any one year. Before promulgating any regulation for which a written statement is needed, section 205 of the UMRA generally requires EPA to identify and consider a reasonable number of regulatory alternatives and adopt the least costly, most cost-effective or least burdensome alternative that achieves the objectives of the rule. The provisions of section 205 do not apply when they are inconsistent with applicable law. Moreover, section 205 allows an Agency to adopt an alternative other than the least costly, most cost-effective or least burdensome alternative if the Administrator publishes with the final rule an explanation why that alternative was not adopted. Before EPA establishes any regulatory requirements that may significantly or uniquely affect small governments, including tribal governments, it must have developed under section 203 of the UMRA a small government Agency plan. The plan must provide for notifying potentially affected small governments, enabling officials of the affected small governments to have meaningful and timely input in the development of regulatory proposals with significant Federal intergovernmental mandates, and EPA informing, educating, and advising small governments on compliance with the regulatory requirements.

Today's rule contains no Federal mandates (under the regulatory provisions of Title II of the Unfunded Mandates Reform Act (UMRA)) for State, local, or tribal governments or the private sector. Today's rule imposes no enforceable duty on any State, local or Tribal governments or the private sector; rather, the CTR promulgates ambient water quality criteria which, when combined with State-adopted uses, will create water quality standards for those water bodies with adopted uses. The State will then use these resulting water quality standards in implementing its existing water quality control programs. Thus, today's rule is not subject to the requirements of sections 202 and 205 of the UMRA.

EPA has determined that this rule contains no regulatory requirements that might significantly or uniquely affect small governments. This rule establishes ambient water quality criteria which, by themselves do not directly impact any entity. The State will implement these criteria by ensuring that NPDES permits result in discharges that will meet these criteria. In so doing, the State will have considerable discretion. Until the State implements these water quality standards, there will be no effect of this rule on any entity. Thus, today's rule is not subject to the requirements of section 203 of UMRA.

K. Regulatory Flexibility Act

The Regulatory Flexibility Act generally requires Federal agencies to prepare a regulatory flexibility analysis of any rule subject to notice and comment rulemaking requirements under the Administrative Procedure Act or any other statute unless the Agency certifies that the rule will not have a significant economic impact of a substantial number of small entities. Small entities include small businesses, small organizations, and small governmental jurisdictions. For purposes of assessing the impacts of today's rule on small entities, small entity is defined as: (1) A small business according to RFA default definitions for small businesses (based on SBA size

standards); (2) a small governmental jurisdiction that is a government of a city, county, town, school district or special district with a population of less than 50,000; and (3) a small organization that is any not-for-profit enterprise which is independently owned and operated and is not dominant in its field.

After considering the economic impacts of today's final rule on small entities, I certify that this action will not have a significant economic impact on a substantial number of small entities. This final rule will not impose any requirements on small entities.

Under the CWA water quality standards program, States must adopt water quality standards for their waters that must be submitted to EPA for approval. If the Agency disapproves a State standard and the State does not adopt appropriate revisions to address EPA's disapproval, EPA must promulgate standards consistent with the statutory requirements. EPA has authority to promulgate criteria or standards in any case where the Administrator determines that a revised or new standard is necessary to meet the requirements of the Act. These State standards (or EPA-promulgated standards) are implemented through various water quality control programs including the National Pollutant Discharge Elimination System (NPDES) program that limits discharges to navigable waters except in compliance with an EPA permit or permit issued under an approved State NPDES program. The CWA requires that all NPDES permits must include any limits on discharges that are necessary to meet State water quality standards.

Thus, under the CWA, EPA's promulgation of water quality criteria or standards establishes standards that the State, in turn, implements through the NPDES permit process. The State has considerable discretion in deciding how to meet the water quality standards and in developing discharge limits as needed to meet the standards. In circumstances where there is more than one discharger to a water body that is subject to water quality standards or criteria, a State also has discretion in deciding on the appropriate limits for the different dischargers. While the State's implementation of federally-promulgated water quality criteria or standards may result indirectly in new or revised discharge limits for small entities, the criteria or standards themselves do not apply to any discharger, including small entities.

Today's rule, as explained above, does not itself establish any requirements that are applicable to small entities. As a result of EPA's action here, the State of California will need to ensure that permits it issues include limits as necessary to meet the water quality standards established by the criteria in today's rule. In so doing, the State will have a number of discretionary choices associated with permit writing. While California's implementation of today's rule may ultimately result in some new or revised permit conditions for some dischargers, including small entities, EPA's action today does not impose any of these as yet unknown requirements on small entities.

The RFA requires analysis of the economic impact of a rule only on the small entities subject to the rule's requirements. Courts have consistently held that the RFA imposes no obligation on an Agency to prepare a small entity analysis of the effect of a rule on entities not regulated by the rule. *Motor & Equip. Mrfrs. Ass'n* v. *Nichols,* 142 F.3d 449, 467 & n.18 (D.C. Cir. 1998)(quoting *United States Distribution Companies* v. *FERC,* 88 F.3d 1105, 1170 (D.C. Cir. 1996); see also *American Trucking Association, Inc.* v. *EPA,* 175 F.3d 1027 (D.C. Cir. 1999). This final rule will have a direct effect only on the State of California which is not a small entity under the RFA. Thus, individual dischargers, including small entities, are not directly subject to the requirements of the rule. Moreover, because of California's discretion in implementing these standards, EPA cannot assess the extent to which the promulgation of this rule may subsequently affect any dischargers, including small entities. Consequently, certification under section 605(b) is appropriate. *State of Michigan, et al.* v. *U.S. Environmental Protection Agency,* No. 98–1497 (D.C. Cir. Mar. 3, 2000), slip op. at 41–42.

L. Paperwork Reduction Act

This action requires no new or additional information collection, reporting, or record keeping subject to the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq.*

M. Endangered Species Act

Pursuant to section 7(a) of the Endangered Species Act (ESA), EPA has consulted with the U.S. Fish and Wildlife Service and the U.S. National Marine Fisheries Service (collectively, the Services) concerning EPA's rulemaking action for the State of California. EPA initiated informal consultation in early 1994, and completed formal consultation in April 2000. As a result of the consultation, EPA modified some of the provisions in the final rule.

As part of the consultation process, EPA submitted to the Services a Biological Evaluation for their review in October of 1997. This evaluation found that the proposed CTR was not likely to jeopardize the continued existence of any Federally listed species or result in the destruction or adverse modification of designated critical habitat. In April of 1998, the Services sent EPA a draft Biological Opinion which tentatively found that EPA's proposed rule would jeopardize the continued existence of several Federally listed species and result in the destruction or have adverse effect on designated critical habitat. After lengthy discussions with the Services, EPA agreed to several changes in the final rule and the Services in turn issued a final Biological Opinion finding that EPA's action would not likely jeopardize the continued existence of any Federally listed species or result in the destruction or adverse modification of designated critical habitat. EPA's Biological Evaluation and the Services' final Biological Opinion are contained in the administrative record for today's rule.

In order to ensure the continued protection of Federally listed threatened and endangered species and to protect their critical habitat, EPA agreed to reserve the aquatic life criteria for mercury and the acute freshwater aquatic life criterion for selenium. The Services believe that EPA's proposed criteria are not sufficiently protective of Federally listed species and should not be promulgated. EPA agreed that it would reevaluate these criteria in light of the Services concerns before promulgating them for the State of California. Other commitments made by EPA are described in a letter to the Services dated December 16, 1999; this letter is contained in the administrative record for today's rule.

N. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, as added by the Small Business Regulatory Enforcement Fairness Act of 1996, generally provides that before a rule may take effect, the Agency promulgating the rule must submit a rule report, which includes a copy of the rule, to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. A major rule cannot take effect until 60 days after it is published in the **Federal Register**. This rule is not a major rule as defined

by 5 U.S.C. 804(2). This rule will be effective May 18, 2000.

O. Executive Order 13084, Consultation and Coordination With Indian Tribal Governments

Under Executive Order 13084, EPA may not issue a regulation that is not required by statute, that significantly or uniquely affects the communities of Indian tribal governments, and that imposes substantial direct compliance costs on those communities, unless the Federal government provides the funds necessary to pay the direct compliance costs incurred by the tribal governments, or EPA consults with those governments. If EPA complies by consulting, Executive Order 13084 requires EPA to provide to the Office of Management and Budget, in a separately identified section of the preamble to the rule, a description of the extent of EPA's prior consultation with representatives of affected tribal governments, a summary of the nature of their concerns, and a statement supporting the need to issue the regulation. In addition, Executive Order 13084 requires EPA to develop an effective process permitting elected officials and other representatives of Indian tribal governments ''to provide meaningful and timely input in the development of regulatory policies on matters that significantly or uniquely affect their communities.''

Today's rule does not significantly or uniquely affect the communities of Indian tribal governments nor does it impose substantial direct compliance cots on them. Today's rule will only address priority toxic pollutant water quality criteria for the State of California and does not apply to waters in Indian country. Accordingly, the requirements of section 3(b) of Executive Order 13084 do not apply to this rule.

P. National Technology Transfer and Advancement Act

Section 12(d) of the National Technology Transfer and Advancement Act of 1995 (''NTTAA''), Public Law No. 104–113, section 12(d) (15 U.S.C. 272 note) directs EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or otherwise impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, and business practices) that are developed or adopted by voluntary consensus standards bodies. The NTTAA directs EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards.

This final rule does not involve technical standards. Therefore, EPA did not consider the use of any voluntary consensus standards.

Q. Executive Order 13132 on Federalism

Executive Order 13132, entitled ''Federalism'' (64 FR 43255, August 10, 1999), requires EPA to develop an accountable process to ensure ''meaningful and timely input by State and local officials in the development of regulatory policies that have federalism implications.'' ''Policies that have federalism implications'' is defined in the Executive Order to include regulations that have ''substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.''

Under section 6 of Executive Order 13132, EPA may not issue a regulation that has federalism implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the Federal government provides the funds necessary to pay the direct compliance costs incurred by State and local governments, or EPA consults with State and local officials early in the process of developing the proposed regulation. EPA also may not issue a regulation that has federalism implications and that preempts State law, unless the Agency consults with State and local officials early in the process of developing the proposed regulation.

This final rule does not have federalism implications. It will not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132. The rule does not affect the nature of the relationship between EPA and States generally, for the rule only applies to water bodies in California. Further, the rule will not substantially affect the relationship of EPA and the State of California, or the distribution of power or responsibilities between EPA and the State. The rule does not alter the State's authority to issue NPDES permits or the State's considerable discretion in implementing these criteria. The rule simply implements Clean Water Act section 303(c)(2)(B) requiring numeric ambient water quality criteria for which EPA has issued section 304(a) recommended criteria in a manner that is consistent with previous regulatory guidance that the Agency has issued to implement CWA section 303(c)(2)(B). Further, this rule does not preclude the State from adopting water quality standards that meet the requirements of the CWA. Thus, the requirements of section 6 of the Executive Order do not apply to this rule.

Although section 6 of Executive Order 13132 does not apply to this rule, EPA did consult with State and local government representatives in developing this rule. EPA and the State reached an agreement that to best utilize its respective resources, EPA would promulgate water quality criteria and the State would concurrently work on a plan to implement the criteria. Since the proposal of this rule, EPA has kept State officials fully informed of changes to the proposal. EPA has continued to invite comment from the State on these changes. EPA believes that the final CTR incorporates comments from State officials and staff.

R. Executive Order 13045 on Protection of Children From Environmental Health Risks and Safety Risks

Executive Order 13045: ''Protection of Children from Environmental Health Risks and Safety Risks'' (62 FR 19885, April 23, 1997) applies to any rule that: (1) Is determined to be ''economically significant'' as defined under Executive Order 12866, and (2) concerns an environmental health or safety risk that EPA has reason to believe may have a disproportionate effect on children. If the regulatory action meets both criteria, the Agency must evaluate the environmental health or safety effects of the planned rule on children, and explain why the planned regulation is preferable to other potentially effective and reasonably feasible alternatives considered by the Agency.

While this final rule is not subject to the Executive Order because it is not economically significant as defined in Executive Order 12866, we nonetheless have reason to believe that the environmental health or safety risk addressed by this action may have a disproportionate effect on children. As a matter of EPA policy, we therefore have assessed the environmental health or safety effects of ambient water quality criteria on children. The results of this assessment are contained in section F.3., Human Health Criteria.

List of Subjects in 40 CFR Part 131

Environmental protection, Indians—lands, Intergovernmental relations, Reporting and recordkeeping requirements, Water pollution control.

Dated: April 27, 2000.

Carol Browner,

Administrator.

For the reasons set out in the preamble, part 131 of chapter I of title 40 of the Code of Federal Regulations is amended as follows:

PART 131—WATER QUALITY STANDARDS

1. The authority citation for part 131 continues to read as follows:

Authority: 33 U.S.C. 1251 *et seq.*

Subpart D—[Amended]

2. Section 131.38 is added to subpart D to read as follows:

§ 131.38 Establishment of Numeric Criteria for Priority Toxic Pollutants for the State of California.

(a) *Scope.* This section promulgates criteria for priority toxic pollutants in the State of California for inland surface waters and enclosed bays and estuaries. This section also contains a compliance schedule provision.

(b)(1) Criteria for Priority Toxic Pollutants in the State of California as described in the following table:

BILLING CODE 6560–50–P

A		B Freshwater		C Saltwater		D Human Health (10^{-6} risk for carcinogens) For consumption of:	
# Compound	CAS Number	Criterion Maximum Conc. [d] B1	Criterion Continuous Conc. [d] B2	Criterion Maximum Conc. [d] C1	Criterion Continuous Conc. [d] C2	Water & Organisms (μg/L) D1	Organisms Only (μg/L) D2
1. Antimony	7440360					14 a,s	4300 a,t
2. Arsenic [b]	7440382	340 i,m,w	150 i,m,w	69 i,m	36 i,m		
3. Beryllium	7440417					n	n
4. Cadmium [b]	7440439	4.3 e,i,m,w,x	2.2 e,i,m,w	42 i,m	9.3 i,m	n	n
5a. Chromium (III)	16065831	550 e,i,m,o	180 e,i,m,o			n	n
5b. Chromium (VI) [b]	18540299	16 i,m,w	11 i,m,w	1100 i,m	50 i,m	n	n
6. Copper [b]	7440508	13 e,i,m,w,x	9.0 e,i,m,w	4.8 i,m	3.1 i,m	1300	
7. Lead [b]	7439921	65 e,i,m	2.5 e,i,m	210 i,m	8.1 i,m	n	n
8. Mercury [b]	7439976	[Reserved]	[Reserved]	[Reserved]	[Reserved]	0.050 a	0.051 a
9. Nickel [b]	7440020	470 e,i,m,w	52 e,i,m,w	74 i,m	8.2 i,m	610 a	4600 a
10. Selenium [b]	7782492	[Reserved] p	5.0 q	290 i,m	71 i,m	n	n
11. Silver [b]	7440224	3.4 e,i,m		1.9 i,m			
12. Thallium	7440280					1.7 a,s	6.3 a,t
13. Zinc [b]	7440666	120 e,i,m,w,x	120 e,i,m,w	90 i,m	81 i,m		
14. Cyanide [b]	57125	22 o	5.2 o	1 r	1 r	700 a	220,000 a,j
15. Asbestos	1332214					7,000,000 fibers/L k,s	
16. 2,3,7,8-TCDD (Dioxin)	1746016					0.000000013 c	0.000000014 c
17. Acrolein	107028					320 s	780 t
18. Acrylonitrile	107131					0.059 a,c,s	0.66 a,c,t
19. Benzene	71432					1.2 a,c	71 a,c
20. Bromoform	75252					4.3 a,c	360 a,c
21. Carbon Tetrachloride	56235					0.25 a,c,s	4.4 a,c,t
22. Chlorobenzene	108907					680 a,s	21,000 a,j,t
23. Chlorodibromomethane	124481					0.401 a,c	34 a,c
24. Chloroethane	75003						
25. 2-Chloroethylvinyl Ether	110758						

26. Chloroform	67663					[Reserved]	[Reserved]
27. Dichlorobromomethane	75274					0.56 a,c	46 a,c
28. 1,1-Dichloroethane	75343						
29. 1,2-Dichloroethane	107062					0.38 a,c,s	99 a,c,t
30. 1,1-Dichloroethylene	75354					0.057 a,c,s	3.2 a,c,t
31. 1,2-Dichloropropane	78875					0.52 a	39 a
32. 1,3-Dichloropropylene	542756					10 a,s	1,700 a,t
33. Ethylbenzene	100414					3,100 a,s	29,000 a,t
34. Methyl Bromide	74839					48 a	4,000 a
35. Methyl Chloride	74873					n	n
36. Methylene Chloride	75092					4.7 a,c	1,600 a,c
37. 1,1,2,2-Tetrachloroethane	79345					0.17 a,c,s	11 a,c,t
38. Tetrachloroethylene	127184					0.8 c,s	8.85 c,t
39. Toluene	108883					6,800 a	200,000 a
40. 1,2-Trans-Dichloroethylene	156605					700 a	140,000 a
41. 1,1,1-Trichloroethane	71556					n	n
42. 1,1,2-Trichloroethane	79005					0.60 a,c,s	42 a,c,t
43. Trichloroethylene	79016					2.7 c,s	81 c,t
44. Vinyl Chloride	75014					2 c,s	525 c,t
45. 2-Chlorophenol	95578					120 a	400 a
46. 2,4-Dichlorophenol	120832					93 a,s	790 a,t
47. 2,4-Dimethylphenol	105679					540 a	2,300 a
48. 2-Methyl-4,6-Dinitrophenol	534521					13.4 s	765 t
49. 2,4-Dinitrophenol	51285					70 a,s	14,000 a,t
50. 2-Nitrophenol	88755						
51. 4-Nitrophenol	100027						
52. 3-Methyl-4-Chlorophenol	59507						
53. Pentachlorophenol	87865	19 f,w	15 f,w	13	7.9	0.28 a,c	8.2 a,c,j
54. Phenol	108952					21,000 a	4,600,000 a,j,t
55. 2,4,6-Trichlorophenol	88062					2.1 a,c	6.5 a,c
56. Acenaphthene	83329					1,200 a	2,700 a
57. Acenaphthylene	208968						
58. Anthracene	120127					9,600 a	110,000 a

59. Benzidine	92875					0.00012 a,c,s	0.00054 a,c,t
60. Benzo(a)Anthracene	56553					0.0044 a,c	0.049 a,c
61. Benzo(a)Pyrene	50328					0.0044 a,c	0.049 a,c
62. Benzo(b)Fluoranthene	205992					0.0044 a,c	0.049 a,c
63. Benzo(ghi)Perylene	191242						
64. Benzo(k)Fluoranthene	207089					0.0044 a,c	0.049 a,c
65. Bis(2-Chloroethoxy)Methane	111911						
66. Bis(2-Chloroethyl)Ether	111444					0.031 a,c,s	1.4 a,c,t
67. Bis(2-Chloroisopropyl)Ether	39638329					1,400 a	170,000 a,t
68. Bis(2-Ethylhexyl)Phthalate	117817					1.8 a,c,s	5.9 a,c,t
69. 4-Bromophenyl Phenyl Ether	101553						
70. Butylbenzyl Phthalate	85687					3,000 a	5,200 a
71. 2-Chloronaphthalene	91587					1,700 a	4,300 a
72. 4-Chlorophenyl Phenyl Ether	7005723						
73. Chrysene	218019					0.0044 a,c	0.049 a,c
74. Dibenzo(a,h)Anthracene	53703					0.0044 a,c	0.049 a,c
75. 1,2 Dichlorobenzene	95501					2,700 a	17,000 a
76. 1,3 Dichlorobenzene	541731					400	2,600
77. 1,4 Dichlorobenzene	106467					400	2,600
78. 3,3'-Dichlorobenzidine	91941					0.04 a,c,s	0.077 a,c,t
79. Diethyl Phthalate	84662					23,000 a,s	120,000 a,t
80. Dimethyl Phthalate	131113					313,000 s	2,900,000 t
81. Di-n-Butyl Phthalate	84742					2,700 a,s	12,000 a,t
82. 2,4-Dinitrotoluene	121142					0.11 c,s	9.1 c,t
83. 2,6-Dinitrotoluene	606202						
84 Di-n-Octyl Phthalate	117840						
85. 1,2-Diphenylhydrazine	122667					0.040 a,c,s	0.54 a,c,t
86. Fluoranthene	206440					300 a	370 a
87. Fluorene	86737					1,300 a	14,000 a
88. Hexachlorobenzene	118741					0.00075 a,c	0.00077 a,c
89. Hexachlorobutadiene	87683					0.44 a,c,s	50 a,c,t
90. Hexachlorocyclopentadiene	77474					240 a,s	17,000 a,j,t
91. Hexachloroethane	67721					1.9 a,c,s	8.9 a,c,t

92. Indeno(1,2,3-cd) Pyrene	193395					0.0044 a,c	0.049 a,c
93. Isophorone	78591					8.4 c,s	600 c,t
94. Naphthalene	91203						
95. Nitrobenzene	98953					17 a,s	1,900 a,j,t
96. N-Nitrosodimethylamine	62759					0.00069 a,c,s	8.1 a,c,t
97. N-Nitrosodi-n-Propylamine	621647					0.005 a	1.4 a
98. N-Nitrosodiphenylamine	86306					5.0 a,c,s	16 a,c,t
99. Phenanthrene	85018						
100. Pyrene	129000					960 a	11,000 a
101. 1,2,4-Trichlorobenzene	120821						
102. Aldrin	309002	3 g		1.3 g		0.00013 a,c	0.00014 a,c
103. alpha-BHC	319846					0.0039 a,c	0.013 a,c
104. beta-BHC	319857					0.014 a,c	0.046 a,c
105. gamma-BHC	58899	0.95 w		0.16 g		0.019 c	0.063 c
106. delta-BHC	319868						
107. Chlordane	57749	2.4 g	0.0043 g	0.09 g	0.004 g	0.00057 a,c	0.00059 a,c
108. 4,4'-DDT	50293	1.1 g	0.001 g	0.13 g	0.001 g	0.00059 a,c	0.00059 a,c
109. 4,4'-DDE	72559					0.00059 a,c	0.00059 a,c
110. 4,4'-DDD	72548					0.00083 a,c	0.00084 a,c
111. Dieldrin	60571	0.24 w	0.056 w	0.71 g	0.0019 g	0.00014 a,c	0.00014 a,c
112. alpha-Endosulfan	959988	0.22 g	0.056 g	0.034 g	0.0087 g	110 a	240 a
113. beta-Endosulfan	33213659	0.22 g	0.056 g	0.034 g	0.0087 g	110 a	240 a
114. Endosulfan Sulfate	1031078					110 a	240 a
115. Endrin	72208	0.086 w	0.036 w	0.037 g	0.0023 g	0.76 a	0.81 a,j
116. Endrin Aldehyde	7421934					0.76 a	0.81 a,j
117. Heptachlor	76448	0.52 g	0.0038 g	0.053 g	0.0036 g	0.00021 a,c	0.00021 a,c
118. Heptachlor Epoxide	1024573	0.52 g	0.0038 g	0.053 g	0.0036 g	0.00010 a,c	0.00011 a,c
119-125. Polychlorinated biphenyls (PCBs)			0.014 u		0.03 u	0.00017 c,v	0.00017 c,v
126. Toxaphene	8001352	0.73	0.0002	0.21	0.0002	0.00073 a,c	0.00075 a,c
Total Number of Criteria [h]		22	21	22	20	92	90

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Footnotes to Table in Parargraph (b)(1):

a. Criteria revised to reflect the Agency q1* or RfD, as contained in the Integrated Risk Information System (IRIS) as of October 1, 1996. The fish tissue bioconcentration factor (BCF) from the 1980 documents was retained in each case.

b. Criteria apply to California waters except for those waters subject to objectives in Tables III–2A and III–2B of the San Francisco Regional Water Quality Control Board's (SFRWQCB) 1986 Basin Plan, that were adopted by the SFRWQCB and the State Water Resources Control Board, approved by EPA, and which continue to apply.

c. Criteria are based on carcinogenicity of 10 (-6) risk.

d. Criteria Maximum Concentration (CMC) equals the highest concentration of a pollutant to which aquatic life can be exposed for a short period of time without deleterious effects. Criteria Continuous Concentration (CCC) equals the highest concentration of a pollutant to which aquatic life can be exposed for an extended period of time (4 days) without deleterious effects. ug/L equals micrograms per liter.

e. Freshwater aquatic life criteria for metals are expressed as a function of total hardness (mg/L) in the water body. The equations are provided in matrix at paragraph (b)(2) of this section. Values displayed above in the matrix correspond to a total hardness of 100 mg/l.

f. Freshwater aquatic life criteria for pentachlorophenol are expressed as a function of pH, and are calculated as follows: Values displayed above in the matrix correspond to a pH of 7.8. CMC = exp(1.005(pH) − 4.869). CCC = exp(1.005(pH) − 5.134).

g. This criterion is based on 304(a) aquatic life criterion issued in 1980, and was issued in one of the following documents: Aldrin/Dieldrin (EPA 440/5–80–019), Chlordane (EPA 440/5–80–027), DDT (EPA 440/5–80–038), Endosulfan (EPA 440/5–80–046), Endrin (EPA 440/5–80–047), Heptachlor (440/5–80–052), Hexachlorocyclohexane (EPA 440/5–80–054), Silver (EPA 440/5–80–071). The Minimum Data Requirements and derivation procedures were different in the 1980 Guidelines than in the 1985 Guidelines. For example, a ''CMC'' derived using the 1980 Guidelines was derived to be used as an instantaneous maximum. If assessment is to be done using an averaging period, the values given should be divided by 2 to obtain a value that is more comparable to a CMC derived using the 1985 Guidelines.

h. These totals simply sum the criteria in each column. For aquatic life, there are 23 priority toxic pollutants with some type of freshwater or saltwater, acute or chronic criteria. For human health, there are 92 priority toxic pollutants with either ''water + organism'' or ''organism only'' criteria. Note that these totals count chromium as one pollutant even though EPA has developed criteria based on two valence states. In the matrix, EPA has assigned numbers 5a and 5b to the criteria for chromium to reflect the fact that the list of 126 priority pollutants includes only a single listing for chromium.

i. Criteria for these metals are expressed as a function of the water-effect ratio, WER, as defined in paragraph (c) of this section. CMC = column B1 or C1 value x WER; CCC = column B2 or C2 value x WER.

j. No criterion for protection of human health from consumption of aquatic organisms (excluding water) was presented in the 1980 criteria document or in the 1986 Quality Criteria for Water. Nevertheless, sufficient information was presented in the 1980 document to allow a calculation of a criterion, even though the results of such a calculation were not shown in the document.

k. The CWA 304(a) criterion for asbestos is the MCL.

l. [Reserved]

m. These freshwater and saltwater criteria for metals are expressed in terms of the dissolved fraction of the metal in the water column. Criterion values were calculated by using EPA's Clean Water Act 304(a) guidance values (described in the total recoverable fraction) and then applying the conversion factors in § 131.36(b)(1) and (2).

n. EPA is not promulgating human health criteria for these contaminants. However, permit authorities should address these contaminants in NPDES permit actions using the State's existing narrative criteria for toxics.

o. These criteria were promulgated for specific waters in California in the National Toxics Rule (''NTR''), at § 131.36. The specific waters to which the NTR criteria apply include: Waters of the State defined as bays or estuaries and waters of the State defined as inland, i.e., all surface waters of the State not ocean waters. These waters specifically include the San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta. This section does not apply instead of the NTR for this criterion.

p. A criterion of 20 ug/l was promulgated for specific waters in California in the NTR and was promulgated in the total recoverable form. The specific waters to which the NTR criterion applies include: Waters of the San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta; and waters of Salt Slough, Mud Slough (north) and the San Joaquin River, Sack Dam to the mouth of the Merced River. This section does not apply instead of the NTR for this criterion. The State of California adopted and EPA approved a site specific criterion for the San Joaquin River, mouth of Merced to Vernalis; therefore, this section does not apply to these waters.

q. This criterion is expressed in the total recoverable form. This criterion was promulgated for specific waters in California in the NTR and was promulgated in the total recoverable form. The specific waters to which the NTR criterion applies include: Waters of the San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta; and waters of Salt Slough, Mud Slough (north) and the San Joaquin River, Sack Dam to Vernalis. This criterion does not apply instead of the NTR for these waters. This criterion applies to additional waters of the United States in the State of California pursuant to 40 CFR 131.38(c). The State of California adopted and EPA approved a site-specific criterion for the Grassland Water District, San Luis National Wildlife Refuge, and the Los Banos State Wildlife Refuge; therefore, this criterion does not apply to these waters.

r. These criteria were promulgated for specific waters in California in the NTR. The specific waters to which the NTR criteria apply include: Waters of the State defined as bays or estuaries including the San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta. This section does not apply instead of the NTR for these criteria.

s. These criteria were promulgated for specific waters in California in the NTR. The specific waters to which the NTR criteria apply include: Waters of the Sacramento-San Joaquin Delta and waters of the State defined as inland (*i.e.,* all surface waters of the State not bays or estuaries or ocean) that include a MUN use designation. This section does not apply instead of the NTR for these criteria.

t. These criteria were promulgated for specific waters in California in the NTR. The specific waters to which the NTR criteria apply include: Waters of the State defined as bays and estuaries including San Francisco Bay upstream to and including Suisun Bay and the Sacramento-San Joaquin Delta; and waters of the State defined as inland (i.e., all surface waters of the State not bays or estuaries or ocean) without a MUN use designation. This section does not apply instead of the NTR for these criteria.

u. PCBs are a class of chemicals which include aroclors 1242, 1254, 1221, 1232, 1248, 1260, and 1016, CAS numbers 53469219, 11097691, 11104282, 11141165, 12672296, 11096825, and 12674112, respectively. The aquatic life criteria apply to the sum of this set of seven aroclors.

v. This criterion applies to total PCBs, e.g., the sum of all congener or isomer or homolog or aroclor analyses.

w. This criterion has been recalculated pursuant to the 1995 Updates: Water Quality Criteria Documents for the Protection of Aquatic Life in Ambient Water, Office of Water, EPA–820-B–96–001, September 1996. See also Great Lakes Water Quality Initiative Criteria Documents for the Protection of Aquatic Life in Ambient Water, Office of Water, EPA–80–B–95–004, March 1995.

x. The State of California has adopted and EPA has approved site specific criteria for the Sacramento River (and tributaries) above Hamilton City; therefore, these criteria do not apply to these waters.

General Notes to Table in Paragraph (b)(1)

1. The table in this paragraph (b)(1) lists all of EPA's priority toxic pollutants whether or not criteria guidance are available. Blank spaces indicate the absence of national section 304(a) criteria guidance. Because of variations in chemical nomenclature systems, this listing of toxic pollutants does not duplicate the listing in Appendix A to 40 CFR Part 423–126 Priority Pollutants. EPA has added the Chemical Abstracts Service (CAS) registry numbers, which provide a unique identification for each chemical.

2. The following chemicals have organoleptic-based criteria recommendations that are not included on this chart: zinc, 3-methyl-4-chlorophenol.

3. Freshwater and saltwater aquatic life criteria apply as specified in paragraph (c)(3) of this section.

(2) Factors for Calculating Metals Criteria. Final CMC and CCC values should be rounded to two significant figures.

(i) $CMC = WER \times (Acute\ Conversion\ Factor) \times (\exp\{m_A[\ln(hardness)]+b_A\})$

(ii) $CCC = WER \times (Acute\ Conversion\ Factor) \times (\exp\{m_C[\ln(hardness)]+b_C\})$

(iii) Table 1 to paragraph (b)(2) of this section:

Metal	m_A	b_A	m_C	b_C
Cadmium	1.128	−3.6867	0.7852	−2.715
Copper	0.9422	−1.700	0.8545	−1.702
Chromium (III)	0.8190	3.688	0.8190	1.561
Lead	1.273	−1.460	1.273	−4.705
Nickel	0.8460	2.255	0.8460	0.0584
Silver	1.72	−6.52		
Zinc	0.8473	0.884	0.8473	0.884

Note to Table 1: The term ''exp'' represents the base e exponential function.

(iv) Table 2 to paragraph (b)(2) of this section:

Metal	Conversion factor (CF) for freshwater acute criteria	CF for freshwater chronic criteria	CF for saltwater acute criteria	CF [a] for saltwater chronic criteria
Antimony	[d]	[d]	[d]	[d]
Arsenic	1.000	1.000	1.000	1.000
Beryllium	[d]	[d]	[d]	[d]
Cadmium	[b] 0.944	[b] 0.909	0.994	0.994
Chromium (III)	0.316	0.860	[d]	[d]
Chromium (VI)	0.982	0.962	0.993	0.993
Copper	0.960	0.960	0.83	0.83
Lead	[b] 0.791	[b] 0.791	0.951	0.951
Mercury	.....	.....	.....	.....
Nickel	0.998	0.997	0.990	0.990
Selenium	.....	[c]	0.998	0.998
Silver	0.85	[d]	0.85	[d]
Thallium	[d]	[d]	[d]	[d]
Zinc	0.978	0.986	0.946	0.946

Footnotes to Table 2 of Paragraph (b)(2):

[a] Conversion Factors for chronic marine criteria are not currently available. Conversion Factors for acute marine criteria have been used for both acute and chronic marine criteria.

[b] Conversion Factors for these pollutants in freshwater are hardness dependent. CFs are based on a hardness of 100 mg/l as calcium carbonate ($CaCO_3$). Other hardness can be used; CFs should be recalculated using the equations in table 3 to paragraph (b)(2) of this section.

[c] Bioaccumulative compound and inappropriate to adjust to percent dissolved.

[d] EPA has not published an aquatic life criterion value.

Note to Table 2 of Paragraph (b)(2): The term ''Conversion Factor'' represents the recommended conversion factor for converting a metal criterion expressed as the total recoverable fraction in the water column to a criterion expressed as the dissolved fraction in the water column. See ''Office of Water Policy and Technical Guidance on Interpretation and Implementation of Aquatic Life Metals Criteria'', October 1, 1993, by Martha G. Prothro, Acting Assistant Administrator for Water available from Water Resource Center, USEPA, Mailcode RC4100, M Street SW, Washington, DC, 20460 and the note to § 131.36(b)(1).

(v) Table 3 to paragraph (b)(2) of this section:

	Acute	Chronic
Cadmium	CF=1.136672—[(ln {hardness}) (0.041838)]	CF = 1.101672—[(ln {hardness})(0.041838)]
Lead	CF=1.46203—[(ln {hardness})(0.145712)]	CF = 1.46203—[(ln {hardness})(0.145712)]

(c) *Applicability.* (1) The criteria in paragraph (b) of this section apply to the State's designated uses cited in paragraph (d) of this section and apply concurrently with any criteria adopted by the State, except when State regulations contain criteria which are more stringent for a particular parameter and use, or except as provided in footnotes p, q, and x to the table in paragraph (b)(1) of this section.

(2) The criteria established in this section are subject to the State's general rules of applicability in the same way and to the same extent as are other Federally-adopted and State-adopted numeric toxics criteria when applied to the same use classifications including mixing zones, and low flow values below which numeric standards can be exceeded in flowing fresh waters.

(i) For all waters with mixing zone regulations or implementation procedures, the criteria apply at the appropriate locations within or at the boundary of the mixing zones; otherwise the criteria apply throughout the water body including at the point of discharge into the water body.

(ii) The State shall not use a low flow value below which numeric standards can be exceeded that is less stringent than the flows in Table 4 to paragraph (c)(2) of this section for streams and rivers.

(iii) Table 4 to paragraph (c)(2) of this section:

Criteria	Design flow
Aquatic Life Acute Criteria (CMC).	1 Q 10 or 1 B 3
Aquatic Life Chronic Criteria (CCC).	7 Q 10 or 4 B 3
Human Health Criteria.	Harmonic Mean Flow

Note to Table 4 of Paragraph (c)(2): 1. CMC (Criteria Maximum Concentration) is the water quality criteria to protect against acute effects in aquatic life and is the highest instream concentration of a priority toxic pollutant consisting of a short-term average not to be exceeded more than once every three years on the average.

2. CCC (Continuous Criteria Concentration) is the water quality criteria to protect against chronic effects in aquatic life and is the highest in stream concentration of a priority toxic pollutant consisting of a 4-day average not to be exceeded more than once every three years on the average.

3. 1 Q 10 is the lowest one day flow with an average recurrence frequency of once in 10 years determined hydrologically.

4. 1 B 3 is biologically based and indicates an allowable exceedence of once every 3 years. It is determined by EPA's computerized method (DFLOW model).

5. 7 Q 10 is the lowest average 7 consecutive day low flow with an average recurrence frequency of once in 10 years determined hydrologically.

6. 4 B 3 is biologically based and indicates an allowable exceedence for 4 consecutive days once every 3 years. It is determined by EPA's computerized method (DFLOW model).

(iv) If the State does not have such a low flow value below which numeric standards do not apply, then the criteria included in paragraph (d) of this section apply at all flows.

(v) If the CMC short-term averaging period, the CCC four-day averaging period, or once in three-year frequency is inappropriate for a criterion or the site to which a criterion applies, the State may apply to EPA for approval of an alternative averaging period, frequency, and related design flow. The State must submit to EPA the bases for any alternative averaging period, frequency, and related design flow. Before approving any change, EPA will publish for public comment, a document proposing the change.

(3) The freshwater and saltwater aquatic life criteria in the matrix in paragraph (b)(1) of this section apply as follows:

(i) For waters in which the salinity is equal to or less than 1 part per thousand 95% or more of the time, the applicable criteria are the freshwater criteria in Column B;

(ii) For waters in which the salinity is equal to or greater than 10 parts per thousand 95% or more of the time, the applicable criteria are the saltwater criteria in Column C except for selenium in the San Francisco Bay estuary where the applicable criteria are the freshwater criteria in Column B (refer to footnotes p and q to the table in paragraph (b)(1) of this section); and

(iii) For waters in which the salinity is between 1 and 10 parts per thousand as defined in paragraphs (c)(3)(i) and (ii) of this section, the applicable criteria are the more stringent of the freshwater or saltwater criteria. However, the Regional Administrator may approve the use of the alternative freshwater or saltwater criteria if scientifically defensible information and data demonstrate that on a site-specific basis the biology of the water body is dominated by freshwater aquatic life and that freshwater criteria are more appropriate; or conversely, the biology of the water body is dominated by saltwater aquatic life and that saltwater criteria are more appropriate. Before approving any change, EPA will publish for public comment a document proposing the change.

(4) *Application of metals criteria.* (i) For purposes of calculating freshwater aquatic life criteria for metals from the equations in paragraph (b)(2) of this section, for waters with a hardness of 400 mg/l or less as calcium carbonate, the actual ambient hardness of the surface water shall be used in those equations. For waters with a hardness of over 400 mg/l as calcium carbonate, a hardness of 400 mg/l as calcium carbonate shall be used with a default Water-Effect Ratio (WER) of 1, or the actual hardness of the ambient surface water shall be used with a WER. The same provisions apply for calculating the metals criteria for the comparisons provided for in paragraph (c)(3)(iii) of this section.

(ii) The hardness values used shall be consistent with the design discharge conditions established in paragraph (c)(2) of this section for design flows and mixing zones.

(iii) The criteria for metals (compounds #1—#13 in the table in paragraph (b)(1) of this section) are expressed as dissolved except where otherwise noted. For purposes of calculating aquatic life criteria for metals from the equations in footnote i to the table in paragraph (b)(1) of this section and the equations in paragraph (b)(2) of this section, the water effect ratio is generally computed as a specific pollutant's acute or chronic toxicity value measured in water from the site covered by the standard, divided by the respective acute or chronic toxicity value in laboratory dilution water. To use a water effect ratio other than the default of 1, the WER must be determined as set forth in Interim Guidance on Determination and Use of Water Effect Ratios, U.S. EPA Office of Water, EPA–823–B–94–001, February 1994, or alternatively, other scientifically defensible methods adopted by the State as part of its water quality standards program and approved by EPA. For calculation of criteria using site-specific values for both the hardness and the water effect ratio, the hardness used in the equations in paragraph (b)(2) of this section must be determined as required in paragraph (c)(4)(ii) of this section. Water hardness must be calculated from the measured calcium and magnesium ions present, and the ratio of calcium to magnesium should be approximately the same in standard laboratory toxicity testing water as in the site water.

(d)(1) Except as specified in paragraph (d)(3) of this section, all waters assigned any aquatic life or human health use classifications in the Water Quality Control Plans for the various Basins of the State (''Basin Plans'') adopted by the California State Water Resources Control Board (''SWRCB''), except for ocean waters covered by the Water Quality Control Plan for Ocean Waters of California (''Ocean Plan'') adopted by the SWRCB with resolution Number 90–27 on March 22, 1990, are subject to the criteria in paragraph (d)(2) of this section, without exception. These criteria apply to waters identified in the Basin Plans. More particularly, these criteria apply to waters identified in the Basin Plan chapters designating beneficial uses for waters within the region. Although the State has adopted several use designations for each of these waters, for purposes of this action, the specific standards to be applied in paragraph (d)(2) of this section are based on the presence in all waters of some aquatic life designation and the presence or absence of the MUN use designation (municipal and domestic supply). (See Basin Plans for more detailed use definitions.)

(2) The criteria from the table in paragraph (b)(1) of this section apply to the water and use classifications defined in paragraph (d)(1) of this section as follows:

Water and use classification	Applicable criteria
(i) All inland waters of the United States or enclosed bays and estuaries that are waters of the United States that include a MUN use designation.	(A) Columns B1 and B2—all pollutants (B) Columns C1 and C2—all pollutants (C) Column D1—all pollutants
(ii) All inland waters of the United States or enclosed bays and estuaries that are waters of the United States that do not include a MUN use designation.	(A) Columns B1 and B2—all pollutants (B) Columns C1 and C2—all pollutants (C) Column D2—all pollutants

(3) Nothing in this section is intended to apply instead of specific criteria, including specific criteria for the San Francisco Bay estuary, promulgated for California in the National Toxics Rule at § 131.36.

(4) The human health criteria shall be applied at the State-adopted 10 (−6) risk level.

(5) Nothing in this section applies to waters located in Indian Country.

(e)*Schedules of compliance.* (1) It is presumed that new and existing point source dischargers will promptly comply with any new or more restrictive water quality-based effluent limitations (''WQBELs'') based on the water quality criteria set forth in this section.

(2) When a permit issued on or after May 18, 2000 to a new discharger contains a WQBEL based on water quality criteria set forth in paragraph (b) of this section, the permittee shall comply with such WQBEL upon the commencement of the discharge. A new discharger is defined as any building, structure, facility, or installation from which there is or may be a ''discharge of pollutants'' (as defined in 40 CFR 122.2) to the State of California's inland surface waters or enclosed bays and estuaries, the construction of which commences after May 18, 2000.

(3) Where an existing discharger reasonably believes that it will be infeasible to promptly comply with a new or more restrictive WQBEL based on the water quality criteria set forth in this section, the discharger may request approval from the permit issuing authority for a schedule of compliance.

(4) A compliance schedule shall require compliance with WQBELs based on water quality criteria set forth in paragraph (b) of this section as soon as possible, taking into account the dischargers' technical ability to achieve compliance with such WQBEL.

(5) If the schedule of compliance exceeds one year from the date of permit issuance, reissuance or modification, the schedule shall set forth interim requirements and dates for their achievement. The dates of completion between each requirement may not exceed one year. If the time necessary for completion of any requirement is more than one year and is not readily divisible into stages for completion, the permit shall require, at a minimum, specified dates for annual submission of progress reports on the status of interim requirements.

(6) In no event shall the permit issuing authority approve a schedule of compliance for a point source discharge which exceeds five years from the date of permit issuance, reissuance, or modification, whichever is sooner. Where shorter schedules of compliance are prescribed or schedules of compliance are prohibited by law, those provisions shall govern.

(7) If a schedule of compliance exceeds the term of a permit, interim permit limits effective during the permit shall be included in the permit and addressed in the permit's fact sheet or statement of basis. The administrative record for the permit shall reflect final permit limits and final compliance dates. Final compliance dates for final permit limits, which do not occur during the term of the permit, must occur within five years from the date of issuance, reissuance or modification of the permit which initiates the compliance schedule. Where shorter schedules of compliance are prescribed or schedules of compliance are prohibited by law, those provisions shall govern.

(8) The provisions in this paragraph (e), Schedules of compliance, shall expire on May 18, 2005.

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IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

Nos. 93-35973 & 93-36000

DIOXIN/ORGANOCHLORINE CENTER, et al.,

Plaintiffs-Appellants, and

LONGVIEW FIBRE CO., et al.,

Plaintiffs-Intervenors and Cross-Appellants,

v.

CHUCK CLARKE, Regional Administrator, and the UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Defendants-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF WASHINGTON

BRIEF FOR THE DEFENDANTS-APPELLEES

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May 31, 1994

TABLE OF CONTENTS

TABLE OF AUTHORITIES

GLOSSARY

As used in this brief, the following abbreviations and short forms have the meanings indicated below:

APA	Administrative Procedure Act, 5 U.S.C. §§ 701-06
AR No.	Administrative Record item number as listed in EPA's Certified Index to the Administrative Record
BAT	best available technology economically achievable
BCF	bioconcentration factor
BEF	bioaccumulation equivalency factor
BCT	best conventional pollution control technology
BMPs	best management practices
BPJ	best professional judgment
BPT	best practicable control technology currently available
CDDs	chlorinated dibenzo-p-dioxins
CDFs	chlorinated dibenzo-furans
CR No.	Clerk's Record Number. Refers to the item number on the District Court Clerk's official docket sheet.
CRITFC	Columbia River Intertribal Fish Commission
CWA or the Act	Clean Water Act, 33 U.S.C. §§ 1251-1387
dioxin	2,3,7,8-tetrachlorodibenzo-p-dioxin
DOC	Plaintiffs-Appellants Dioxin/Organochlorine Center, et al.
DOC Br.	Opening Brief of Plaintiffs-Appellants Dioxin/Organochlorine Center, et al.
DOC ER	Excerpts of Record of Plaintiffs-Appellants Dioxin/Organochlorine Center, et al.
EPA or the Agency	U.S. Environmental Protection Agency

ESA	Endangered Species Act
ICS	individual control strategy
LA	load allocation
Mills or Pulp Mills	Plaintiffs-Intervenors and Cross-Appellants Longview Fibre Co., et al.
Mills Br.	Opening Brief of Plaintiffs-Intervenors and Cross-Appellants Longview Fibre Co., et al.
Mills ER	Excerpts of Record of Appellants Longview Fibre Co., et al.
NPDES	National Pollutant Discharge Elimination System
NPS	nonpoint source
NYDEC	New York Department of Environmental Conservation
PCBs	polychlorinated biphenyls
ppq	parts per quadrillion
ppt	parts per trillion
SER	Defendant-Appellee EPA's Supplemental Excerpts of Record
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCDF	2,3,7,8 tetrachlorodibenzofuran
TEF	toxic equivalency factor
TMDL	Total Maximum Daily Load
USFWS	United States Fish & Wildlife Service
WLA	wasteload allocation
WQL	water quality limited
WQS	water quality standard

ISSUES PRESENTED

1. Whether the Environmental Protection Agency ("EPA") reasonably interpreted the Clean Water Act as authorizing it to calculate a Total Maximum Daily Load ("TMDL") necessary to achieve water quality standards for a highly toxic pollutant, in the absence of national, technology-based effluent limitations for pulp mill discharges of that pollutant.

2. Whether there is sufficient support in the administrative record for EPA's conclusion that the Columbia River TMDL is set at a level that will implement applicable water quality standards with a margin of safety.

STATEMENT OF JURISDICTION

Pursuant to Circuit Rule 28-2.2, appellees provide the following statement regarding jurisdiction:

(a) EPA had jurisdiction under 33 U.S.C. § 1313(d)(2) to issue the TMDL. The district court had jurisdiction under 28 U.S.C. § 1331 and the Administrative Procedure Act, 5 U.S.C. §§ 701 et seq., to review the TMDL.1/

(b) The district court granted EPA's motion for summary judgment on August 10, 1993, and subsequently entered final

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1/ The basis on which the district court exercised jurisdiction may have relevance to plaintiffs' claim for attorneys' fees in the event they prevail on appeal. Contrary to the jurisdictional statement of Dioxin/Organochlorine Center and Columbia River United (collectively, "DOC"), DOC Br. at 1, the court did not possess jurisdiction under the citizen suit provision of the Clean Water Act, 33 U.S.C. § 1365(a), which authorizes suits against EPA's Administrator to compel the Agency to perform an act or duty which is not discretionary. Rather, jurisdiction was present only to review the discretionary content of final agency action, pursuant to the standards of the Administrative Procedure Act.

judgment in favor of EPA pursuant to that order. This Court has jurisdiction to review that judgment under 28 U.S.C. § 1291.

(c) The district court's judgment was entered on August 17, 1993. DOC and Plaintiffs-Intervenors Longview Fibre Co., et al. (the "Pulp Mills"), filed notices of appeal on October 8, 1993, and October 20, 1993, respectively. The notices were timely under Fed. R. App. P. 4(a)(1) & (3).

STATEMENT OF THE CASE

A. Nature of the Case and Disposition Below

This case arises on complaints for judicial review of a final EPA action to establish a Total Maximum Daily Load ("TMDL"), under the Clean Water Act, 33 U.S.C. § 1313(d), for discharges of dioxin to the Columbia River basin in Oregon, Washington and Idaho.[2/] DOC and the Pulp Mills[3/] moved for summary judgment, and Defendants Environmental Protection Agency and Chuck Clarke, Regional Administrator[4/] (collectively "EPA"), filed a cross-

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2/ EPA's decision establishing the TMDL is embodied in a Decision Document appearing in the Pulp Mills' Excerpts of Record ("Mills ER") at 87-127, and in DOC's Excerpts of Record ("DOC ER") at tab ER 47/AR 19(2). That decision is also supported by a Response to Comment Document, Mills ER at 128-59; DOC ER tab ER 47/AR 19(3). "AR" refers to documents as numbered in EPA's Administrative Record, which was filed with the district court as an exhibit, Clerk's Record ("CR") No. 47. For convenience, we provide parallel citations to the Mills ER or EPA's Supplemental Excerpts of Record ("SER"), where included therein.

3/ Although nominally a plaintiff, Intervenor Pope & Talbot, Inc. did not join in the other pulp mills' motion for summary judgment. See CR No. 18. Rather, Pope & Talbot's participation in the district court proceedings was limited to opposing DOC's attempt to invalidate the TMDL. See CR No. 59.

4/ By Order entered March 1, 1994, the Court substituted Gerald Emison, Acting Regional Administrator, for his predecessor in office, Dana A. Rasmussen. Subsequently, on March 7, 1994, Chuck Clarke became Regional Administrator, and he should now be substituted for Mr. Emison pursuant to Fed. R. App. P. 43(c)(1).

motion for summary judgment. The district court denied plaintiffs' motions for summary judgment, and granted summary judgment in favor of EPA in an unreported opinion. CR No. 88, Mills ER 232-49. These consolidated appeals followed.[5/]

B. Statutory and Regulatory Background

1. The NPDES Permit System

The Clean Water Act, 33 U.S.C. §§ 1251-1387 ("CWA" or the "Act"), was adopted "to restore and maintain the chemical, physical, and biological integrity of the Nation's waters." 33 U.S.C. § 1251(a). See Rybachek v. EPA, 904 F.2d 1276, 1282 (9th Cir. 1990). As the cornerstone of the CWA scheme for the control of point source pollution, the Act prohibits the "discharge of any pollutant" except as authorized by a National Pollutant Discharge Elimination System ("NPDES") permit. 33 U.S.C. § 1311(a). The CWA authorizes EPA, or a state approved by EPA to administer its NPDES permit program, to "issue a permit for the discharge of any pollutant," provided that the permit contains conditions that implement various requirements of the Act. 33 U.S.C. § 1342(a)(1).[6/] In authorized states, NPDES permits are issued by the appropriate state agency, but are subject to EPA objection. 33 U.S.C. § 1342(d), 40 C.F.R. § 123.44 (1992).

[5/] Plaintiff-Intervenors Pope & Talbot and Potlatch Corp. did not join in the notice of cross-appeal filed by the other Pulp Mills. CR No. 113, Mills ER 253-54.

[6/] EPA may authorize a state meeting certain requirements to issue NPDES permits. 33 U.S.C. § 1342(b). Oregon and Washington are authorized to administer their own NPDES permit programs; EPA is responsible for issuing permits for point sources in Idaho.

NPDES permits commonly contain numerical limits on the amounts of specified pollutants that may be discharged. See Rybachek, 904 F.2d at 1283. These "effluent limitations" implement both technology-based and water quality-based requirements of the Act. See 33 U.S.C. § 1362(11). Technology-based effluent limitation guidelines are developed by EPA for classes or categories of point sources. 33 U.S.C. § 1314(b). These guidelines represent the degree of control that can be achieved by point sources using various levels of pollution control technology, and are used in establishing enforceable technology-based effluent limitations in NPDES permits. See 33 U.S.C. §§ 1311, 1314; E.I. Du Pont de Nemours & Co. v. Train, 430 U.S. 112, 126-36 (1977). Development and revision of such guidelines is a continuing process. See 33 U.S.C. § 1314(m) (requiring EPA to prepare effluent guideline development plans annually).7/ When EPA has not yet issued national effluent limitation guidelines for a category of point sources, the Agency is authorized under 33 U.S.C. § 1342(a)(1) to develop such limitations for NPDES permits on a case-by-case basis. Natural Resources Defense Council v. Costle, 568 F.2d 1369, 1378 (D.C. Cir. 1977). EPA refers to such permit limits as "Best Professional Judgment" ("BPJ") limits. See Natural Resources Defense Council v. EPA, 863 F.2d 1420, 1424 (9th Cir. 1988).

7/ As of September, 1992, EPA was in the process of developing new or revised effluent guidelines for nine industrial categories (including the pulp and paperboard category), and announced plans to develop an additional 12 effluent guidelines over an 11 year period. 57 Fed. Reg. 41,000 (Sept. 8, 1992).

Congress required NPDES permits to include limitations for conventional pollutants[8/] based upon "best practicable control technology currently available" ("BPT") by July 1, 1977, and upon "best conventional pollution control technology" ("BCT") by March 31, 1989. 33 U.S.C. §§ 1311(b)(1)(A) & (2)(E), 1314(b)(1) & (4). For toxic pollutants such as dioxin[9/] and for non-conventional pollutants,[10/] NPDES permits were to include limitations based upon BPT by July 1, 1977, and limitations based upon "best available technology economically achievable" ("BAT") by March 31, 1989. 33 U.S.C. §§ 1311(b)(1)(A) & (2)(A), 1314(b)(1)-(2), 1342(a). See Rybachek, 904 F.2d at 1283. NPDES permits also must contain limitations more stringent than the technology-based standards if necessary to implement any applicable water quality standard. 33 U.S.C. § 1311(b)(1)(C).

2. Water Quality Standards and TMDLs

Section 303 of the Act, 33 U.S.C. § 1313, requires each state to adopt water quality standards applicable to its intrastate and interstate waters. See 33 U.S.C. § 1313(a)-(c). Water quality standards consist of two principal elements: (1) designated "uses" of the water, such as for public water supply, recreation, or propagation of fish, consistent with the Act's goals as set forth

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8/ "Conventional" pollutants include suspended solids, fecal coliform, biochemical oxygen demand, and pH. See 33 U.S.C. § 1314(a)(4); 40 C.F.R. § 401.16. Unless otherwise noted, all citations to the Code of Federal Regulations refer to the 1992 edition.

9/ Toxic pollutants are identified pursuant to 33 U.S.C. § 1317(a). See 40 C.F.R. § 401.15.

10/ Non-conventional pollutants are all pollutants not classified as either conventional or toxic.

in 33 U.S.C. § 1251(a)(2), see 40 C.F.R. § 130.3, and (2) "criteria" specifying the amounts of various pollutants which may be present in those waters without impairing the designated uses, expressed as numerical concentration limits or in narrative form. 33 U.S.C. § 1313(c)(2)(A). EPA reviews standards adopted by the states to ensure their consistency with the Act's requirements. 33 U.S.C. § 1313(c)(3)-(4).

The Act required EPA and the states to impose, by 1977, effluent limitations necessary to meet water quality standards. 33 U.S.C. § 1311(b)(1)(C). To facilitate imposition of water quality-based effluent limitations where the technology-based effluent limitations required by 1977 were not sufficient, standing alone, to bring polluted waterbodies into attainment with the water quality standards, Congress also established a mechanism for determination of Total Maximum Daily Loads, or "TMDLs." Section 1313(d) creates a systematic means for states to identify and prioritize waters within their boundaries for which the BPT-based effluent limitations required by section 1311(b)(1)(A)-(B) are not stringent enough to implement the applicable water quality standards.11/ States are required to develop TMDLs on a priority basis for each identified waterbody and for each relevant pollu-

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11/ Waters so identified are referred to as "water quality limited segments." 40 C.F.R. § 130.2(j). EPA regulations require establishment of TMDLs where all existing pollution control requirements (including BAT-based limitations, enforceable controls on nonpoint sources, etc.) are inadequate to lead to attainment of standards, 40 C.F.R. § 130.7, thereby ensuring that limited state and federal resources for TMDL development will be addressed to curing water quality impairments.

tant at a level necessary to implement the water quality standards with a margin of safety. 33 U.S.C. § 1313(d)(1)(A), (C).12/

States must submit lists of water quality limited segments to EPA for review every two years, 40 C.F.R. § 130.7(d), and must submit TMDLs developed on a priority basis to EPA from time to time. 33 U.S.C. § 1313(d)(2). If EPA disapproves the list and/or load, it must itself identify water quality limited segments and establish TMDLs as necessary to implement the applicable water quality standards. 33 U.S.C. § 1313(d)(2).

For waterbodies with multiple sources of a particular pollutant, a TMDL provides a mechanism for determining the permissible "loading" from each source necessary for the overall water to meet water quality standards. A TMDL represents the maximum amount of pollutant loadings which can be introduced into a receiving water without violating the standards, taking into account seasonal variations and a margin of safety. 33 U.S.C. § 1313(d)(1)(C). It is the sum of the "load allocations," which are best estimates of the loading attributed to nonpoint sources of pollution or natural background sources, 40 C.F.R. § 130.2(g), and individual wasteload allocations ("WLAs"), which are the portions of a receiving water's loading capacity allocated to specific point sources. 40 C.F.R. § 130.2(h)-(i). Where a TMDL and WLAs have been estab-

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12/ Pursuant to 33 U.S.C. § 1314(a)(2)(D), EPA has identified all pollutants as generally suitable for TMDL development. See 43 Fed. Reg. 60,662 (Dec. 28, 1978).

lished, permits for point sources must be consistent with their requirements. 40 C.F.R. § 122.44(d)(1)(vii)(B).[13/]

3. Additional Controls for Toxic Pollutants

In amending the Clean Water Act in 1987, Congress emphasized attainment of state water quality standards for toxic pollutants. One important component of this emphasis was the establishment of the toxics control program under 33 U.S.C. § 1314(l), in order to identify and control "toxic hotspots." 133 Cong. Rec. 1287 (1987) (statement of Sen. Moynihan); Westvaco Corp. v. EPA, 899 F.2d 1383, 1385 (4th Cir. 1990). To accomplish this purpose, section 1314(l)(1) required each state, by February 1989, to submit three lists of waters to EPA. The only one of the three relevant here is the "B list," listing those waters that the state "does not expect" to achieve applicable water quality standards, after application of technology-based controls, due to discharges of toxic pollutants from point sources. 33 U.S.C. § 1314(l)(1)(B). For each water segment on any of the three lists, the state was required by the same date to submit a "C list" of point sources discharging toxic pollutants "believed to be preventing or impairing . . . water quality." 33 U.S.C. § 1314(l)(1)(C); Natural Resources Defense Council v. EPA, 915 F.2d 1314 (9th Cir. 1990).

Section 1314(l) also required the states to evaluate the dischargers on the C list and submit to EPA, for each such discharger, an individual control strategy ("ICS") which the state had determined would serve to reduce point source discharges of

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13/ Even if a TMDL has not been completed, 33 U.S.C. § 1311(b)(1)(C) requires permits to include limits necessary to implement applicable water quality standards.

toxic pollutants to a degree sufficient to attain water quality standards within three years after the date of the establishment of the ICS. 33 U.S.C. § 1314(l)(1)(D); Westvaco, 899 F.2d at 1385; Natural Resources Defense Council, 915 F.2d at 1323-24. EPA has defined an ICS to be a final or draft NPDES permit, with supporting documentation showing that effluent limits are "consistent with an approved wasteload allocation [under section 1313(d)], or other documentation which shows that applicable water quality standards will be met not later than three years after the individual control strategy is established." 40 C.F.R. § 123.46(c); see also 54 Fed. Reg. 246-58 (Jan. 4, 1989), and 54 Fed. Reg. 23,868, 23,888 (June 2, 1989).

C. The Columbia River TMDL

1. Identification of the Columbia River as Water Quality Limited for Dioxin

2,3,7,8-tetrachlorodibenzo-p-dioxin -- which we will refer to by the shorthand "dioxin" or the acronym "TCDD" -- is "an unusually toxic compound with demonstrated acute, subacute and chronic effects in animals and man." AR No. 107, at C-178, SER 40; CR No. 88 at 2, Mills ER 233. Indeed, it has been identified as "one of the most toxic substances known." AR No. 107, at A-8, SER 19. Exposure can adversely affect the skin, liver, nervous system and immune system. Id. at C-178, SER 40. Dioxin also "displays an unusually high degree of reproductive toxicity." Id. It has been shown to be mutagenic and carcinogenic. Id. at A-8, SER 19; CR No. 88 at 2, Mills ER 233. These findings have led EPA to conclude that dioxin represents a potential hazard to both

aquatic and terrestrial life, and that it is "one of the major concerns for public health." AR No. 107, at A-8, SER 19.

The fact that dioxin can be toxic in minute quantities causes great practical difficulties in detecting and controlling sources of dioxin contamination. It is now known that dioxin is a by-product of, among other things, the bleaching of wood pulp with chlorine or chlorine derivatives. See AR No. 19(1), Mills ER at 83; 58 Fed. Reg. 66,078, 66,092 (Dec. 17, 1993). In the mid-to-late 1980's, EPA undertook an ambitious series of studies in an effort to quantify the extent of dioxin in our nation's waters, particularly as a result of pulp and paper mill production. It was not until 1987 that the first major study, the "Five Mill Study," confirmed that chlorine-bleaching pulp and paper mills were potential sources of dioxin contamination. See CR No. 88 at 6-7, Mills ER 237-38. These findings led EPA to conduct two additional national studies. First, the National Bioaccumulation Study indicated that TCDD was bioaccumulating in (i.e., building up in the tissues of) fish collected downstream from a number of pulp and paper mills. AR No. 105, SER 17; AR No. 19(2) at 2-2, Mills ER 92. The second study, the "104 Mill Study," was conducted jointly with an industry group, and was a greatly expanded survey of dioxin in the wastewater, treatment plant sludge, and pulp of every chlorine-bleaching mill in the country. Completed in 1989, it confirmed that bleached kraft pulp and paper mills are a significant source of TCDD contamination in the Columbia River system. AR No. 19(2) at 2-2, Mills ER 92; AR No. 114, SER 51-54. See also AR Nos. 124, 128.

The plaintiff Pulp Mills own and operate bleached kraft pulp and paper mills which discharge effluent into the Columbia River or its tributaries in Idaho, Oregon and Washington. See AR No. 19(2) at 3-3, Mills ER 96. EPA and the relevant states addressed concerns over the discharge of dioxin from these mills through two complementary programs: the section 1314(l) toxics control program and the section 1313(d) TMDL program. Under the section 1314(l) program for controlling "toxic hot spots," both Oregon and Washington submitted lists identifying the plaintiffs' mills as point sources of dioxin believed to be impairing the water quality of the Columbia River. See 33 U.S.C. § 1314(l)(1)(C); AR No. 19(2) at 3-7, Mills ER 100; AR Nos. 148-49. Thus, under section 1314(l)(1)(D), these states were required to issue ICSs, in the form of NPDES permits, which would reduce these point source discharges of dioxin to a degree sufficient to attain water quality standards. 40 C.F.R. § 123.46(a).

Concurrent with the actions under section 1314(l), the states of Oregon, Washington, and Idaho identified the Columbia River as requiring a TMDL for dioxin under section 1313(d)(1). AR Nos. 32-34, 41, SER 6-9; see also AR Nos. 123, 130. This designation meant that existing effluent limitations and other controls were not stringent enough to achieve the water quality criteria for dioxin. 40 C.F.R. § 130.7(b). After consultation with EPA, the states concluded that EPA should establish the TMDL to assure equitable distribution of the loading capacity of the river among the multiple sources in this interstate basin. In their letters formally identifying the Columbia River as impaired due to dioxin,

the states declined to establish a TMDL and requested that EPA do so. AR Nos. 32-34, SER 6-8. EPA responded by approving the listing of the Columbia River as impaired due to dioxin, disapproving the states' decision not to establish a TMDL, and proceeding to develop the TMDL itself. AR No. 10, SER 1.

2. The Proposed TMDL

On June 14, 1990, EPA published public notice of the proposed TMDL, and invited public comments. AR No. 10(1), 10(2), Mills ER at 1-31. As EPA noted, the focus on toxic pollutants mandated by the 1987 amendment to section 1314(l) supported establishment of the TMDL on an urgent basis. AR No. 10(2) at 4, Mills ER at 8.[14/]

The proposal discussed the steps in the TMDL-setting process and EPA's proposed resolution of various issues. First, EPA determined that applicable water quality criteria for the protection of human health required that long-term dioxin concentration in the river be no greater than 0.013 parts per quadrillion ("ppq"). AR No. 10(2) at 7, Mills ER at 11.[15/] The Agency also concluded that an ambient concentration of 0.013 ppq would protect aquatic life and wildlife, and would therefore implement state narrative water quality standards for aquatic life

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14/ The TMDL would provide a yardstick for evaluating the adequacy of the pulp mill ICSs being developed at the same time by the relevant states. Id. ("Limits included in ICSs, developed under § [1314(l)], must be consistent with waste load allocations (WLAs) where a TMDL has been established.").

15/ At the time, EPA based this determination on Oregon's applicable numeric water quality criterion for dioxin of 0.013 ppq, and Idaho's and Washington's narrative dioxin standards. EPA has since adopted a numeric water quality criterion of 0.013 ppq for Washington and Idaho. See 57 Fed. Reg. 60,848, 60,911, 60,922-23 (Dec. 22, 1992).

and wildlife protection. Declaration of Richard Albright ¶ 6, CR No. 47 Exh. C, SER 65-66.16/

Next, EPA analyzed flow volumes at various points in the river to ascertain its loading capacity, i.e., the greatest amount of dioxin loading that the river could receive without violating the water quality criteria. AR No. 10(2) at 8, Mills ER 12. EPA acknowledged evidence that some dioxin may adhere to particulate matter and settle to the bottom of some rivers, but proposed to make the conservative assumption that no net attenuation occurs, in light of the fact that sedimentation may be offset by a re-suspension of existing sediments. AR No. 10(2) at 12-13, Mills ER 16-17. EPA calculated that the loading capacity of the entire Columbia River was 5.97 milligrams per day. AR No. 10(2) at 8, Mills ER 12.

Second, EPA proposed an allocation of the loading capacity to the various sources of dioxin in the watershed. This involved evaluating the existing loading from all dioxin sources. AR No. 10(2) at 10-12, Mills ER at 14-16. Because chlorine bleaching pulp mills constituted the only source type for which EPA had site specific quantitative information on effluent quality sufficient to establish wasteloads, and were also the source category that EPA believed to be the largest contributor of dioxin to the river, EPA proposed to establish WLAs only for the pulp mills at this

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16/ The district court allowed EPA to supplement the administrative record with Mr. Albright's declaration, finding it admissible as additional information from the agency explaining the basis of its decision. Order entered June 21, 1993, CR No. 80. DOC consented to the admission of this declaration, CR No. 72 at 3, and does not contest its admissibility on appeal.

time, leaving a portion of the loading capacity unallocated to account for other sources, future growth, and a margin of safety. AR No. 10(2) at 18, Mills ER at 22.

EPA's calculation of specific WLAs for the individual mills was influenced by the analytical detection limit for dioxin -- i.e., the smallest concentration of dioxin that can be reliably detected by available methods. AR No. 10(2) at 19, Mills ER at 23. If EPA applied the current general method detection limit of 10 ppq[17/] as a long term average effluent limit at the point of discharge, the cumulative load from pulp mills alone would be more than twice the Columbia River's daily loading capacity. AR No. 10(2) at 19, Mills ER at 23. Because a permit condition set at a level below the general analytical detection limit would make it difficult or impossible to determine compliance, AR No. 10(2) at 20, Mills ER at 24, EPA considered alternative methods for reducing loading from pulp mills without presuming an ability to detect concentrations lower than 10 ppq. One such method was to move the compliance monitoring point upstream in the mills' production processes, to the bleaching plant where dioxin is generated. By limiting average concentrations in the combined bleach plant waste stream to 10 ppq, before dilution later in the pulp mills' production processes, EPA could reduce pulp mill discharges of dioxin to 67 percent of the Columbia River's loading capacity. Id. Finally, EPA determined that by limiting effluent

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17/ The detection limit varies to some extent above and below the 10 ppq value depending on interferences present in the sample and the equipment available to the analytical laboratory performing the analyses. AR No. 19(3) at 2, Mills ER at 129.

concentrations at the pulp mills' bleaching plants to a maximum concentration of 10 ppq rather than a long-term average of 10 ppq, and adjusting for production levels, it could effectively lower cumulative dioxin loading from pulp mills to about 34 percent of the river's capacity. AR No. 10(2) at 21-22, Mills ER at 25-26.

In order to allow a sufficient share of the loading capacity for other types of dischargers and a margin of safety, EPA proposed to adopt the latter method for calculating WLAs for the individual pulp mills. AR No. 10(2) at 24, Mills ER at 28. EPA's public notice of the proposed TMDL specifically requested comment on a number of technical issues, including the adequacy of the margin of safety to be held in reserve for other, unquantified sources. AR No. 10(1) at 4, Mills ER at 4.[18/]

During the development of the TMDL, EPA entered into informal consultation with the U.S. Fish and Wildlife Service ("USFWS") concerning the effects of dioxin on bald eagles. EPA wrote to the USFWS requesting informal consultation on October 17, 1990. AR No. 15, SER 2. The USFWS responded to EPA's consultation request

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18/ EPA received dozens of written comments on the proposed TMDL from the Pulp Mills and other state, industry, tribal, private and environmental interests. AR Nos. 56-59, 61-67, 69-101. The Pulp Mills filed voluminous comments criticizing various aspects of the proposal. AR Nos. 88-91. In particular, the Mills suggested that EPA should have allocated nearly 100 percent of the river's loading capacity to pulp mills. See AR No. 89 at 18-19, Mills ER at 65-66; compare AR No. 88(1) at 19 (advocating that dioxin loading from pulp mills in the Columbia River basin be allocated a cumulative loading of 5.96 mg/day), with AR No. 10(2) at 16, Mills ER at 20 (total loading capacity of Columbia River estimated at 5.97 mg/day). Environmental groups, on the other hand, filed comments alleging that the proposed TMDL would allow too much dioxin loading to the river to protect human health and the environment. They also asked that the TMDL be broadened in scope to address other pollutants that they believed operated with dioxin to create "toxic stress" in the river.

on November 21, 1990, AR No. 103, SER 14-16, and commended EPA's actions in developing a TMDL that would reduce pulp mill discharges of dioxin to the Columbia River by 95 percent. The USFWS also acknowledged that much was unknown about the effect that past discharges of dioxin had had on bald eagles residing in the Columbia River basin. Id.; AR No. 22, SER 4.

3. The Final TMDL

On February 25, 1991, EPA established the final TMDL for discharges of dioxin to the Columbia River. AR No. 19(2), Mills ER 87-127. EPA responded to the major comments received both in the Decision Document and in a supplemental Response to Comments document. AR No. 19(3), Mills ER 128-59. EPA discussed its response to the comments in detail, and explained its chosen course at length.

Although several adjustments were made in response to additional information received, EPA adopted final wasteload allocations generally equivalent to the preferred option in the proposed TMDL, see AR No. 19(2) at 3-8 to 3-9, Mills ER at 101-02, assigning approximately 35 percent of the river's loading capacity to United States pulp mills in the basin. EPA concluded that the Pulp Mills' proposal to allocate 100 percent of the loading capacity to chlorine bleaching pulp mills was inappropriate because it did not account for dioxin loadings from other sources on the river, and would not include a margin of safety to account for uncertainties. AR No. 19(2) at 3-9 to 3-10, Mills ER 102-03.

In developing the final TMDL, EPA concluded that the reduction of the existing dioxin discharges to the Columbia River

basin would not adversely affect any threatened or endangered species. AR Nos. 15, 22, SER 2, 4. The USFWS agreed with this conclusion. AR Nos. 22, 103, SER 4, 14. The USFWS indicated that it did not expect EPA to engage in any further consultation unless additional information became available indicating a potential for dioxin discharges to adversely affect threatened or endangered species. Id.

As required by section 1314(l), the states of Oregon and Washington have since issued NPDES permits consistent with the TMDL to these pulp and paper mills, and EPA has issued such a permit to Potlatch. The permits issued in all three states are undergoing review either at the administrative level or in state court, although the permits issued to the Oregon mills are in effect in the interim.

D. Court Challenges to the TMDL

The Pulp Mills and DOC have launched several diametric attacks on the TMDL. In Longview Fibre Co. v. Rasmussen, 980 F.2d 1307 (9th Cir. 1992), this Court dismissed the Pulp Mills' and DOC's petitions for review of the TMDL for lack of original jurisdiction. Thereafter, DOC filed suit challenging the TMDL in district court, and the Pulp Mills intervened as plaintiffs, raising numerous challenges distinct from those pressed by DOC.[19/] The parties filed cross-motions for summary judgment, and on August 10, 1993, Judge Carolyn Dimmick granted EPA's motion for

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19/ Plaintiff-Intervenor Pope & Talbot, Inc., although nominally joining in the Pulp Mills' complaint in intervention, in fact filed a brief supporting the TMDL and opposing DOC's motion for summary judgment. CR No. 59.

summary judgment, and denied the motions of DOC and the Pulp Mills. CR No. 88, Mills ER 232.

The district court first considered and rejected the Pulp Mills' argument that EPA lacked the statutory authority to establish the TMDL in the absence of technology-based effluent limitations specifically addressing pulp mill discharges of dioxin. CR No. 88 at 4-10, Mills ER 235-41. Recognizing that pulp mill discharges of dioxin were not identified as posing a significant pollution problem until long after technology-based effluent limitations were to have been implemented under the statutory timetable, the court found nothing in the Clean Water Act that mandated delaying water quality-based controls, such as a TMDL, until after establishment and evaluation of technology-based restrictions. CR No. 88 at 7, Mills ER at 238. Instead, the court found that the Act vests EPA with broad authority to accomplish one of the Act's central objectives, the achievement of water quality standards. CR No. 88 at 9, Mills ER 240. The court then rejected several additional arguments which the Pulp Mills do not raise on appeal. CR No. 88 at 10-13, Mills ER 241-44.

DOC claimed, as it does here, that the TMDL fails to provide adequate protection for wildlife and for human populations who consume larger than average amounts of fish from the Columbia River. Turning to those claims, the court found that the administrative record supported EPA's determination that applicable narrative water quality standards were equally stringent to Oregon's numeric criterion of 0.013 ppq. CR No. 88 at 14-15, Mills ER 245-46. The court then reviewed the evidence in the

record and held that EPA's conclusion that a TMDL designed to achieve a 0.013 ppq standard would provide adequate protection for fish and wildlife was not arbitrary or capricious. CR No. 88 at 15-16, Mills ER at 246-47. The court also found adequate support for EPA's judgment that the 0.013 water quality standard provides sufficient protection for certain human populations in the region, such as Native Americans and subsistence fishermen, that eat higher than average amounts of fish. CR No. 88 at 16-17, Mills ER 247-48. Finally, the district court rejected DOC's claim that EPA acted arbitrarily by failing to consider synergistic and additive effects of other pollutants besides dioxin. The court ruled that the Clean Water Act and EPA's implementing regulations authorize the Agency to calculate separate TMDLs for different pollutants, and to prioritize TMDL development to address the worst pollution problems first. CR No. 88 at 17-18, Mills ER 248-49.

Summarizing, the district court concluded that "EPA performed scientifically valid analysis to arrive at the proper total maximum daily load for the River," and that the "considerable number of conservative assumptions incorporated into EPA calculations . . . ensures the margin of safety required by the Clean Water Act." CR No. 88 at 18, Mills ER 249. Following formal entry of the court's judgment for EPA, both DOC and the Pulp Mills filed their notices of appeal.

STANDARD OF REVIEW

This Court reviews a grant of summary judgment de novo to determine whether there are any genuine issues of material fact. Nevada Land Action Ass'n v. United States Forest Service, 8 F.3d

713, 716 (9th Cir. 1993); Norfolk Energy, Inc. v. Hodel, 898 F.2d 1435, 1439 (9th Cir. 1990). In the context of reviewing a decision by an administrative agency, de novo review means that this Court views the case from the same position as the district court. Nevada Land, 8 F.3d at 716; Daly-Murphy v. Winston, 837 F.2d 348, 351 (9th Cir. 1987).

A grant of summary judgment is appropriate if it appears that there are no genuine issues of material fact and that the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); T.W. Elec. Serv., Inc. v. Pacific Elec. Contractors Ass'n, 809 F.2d 626, 630-31 (9th Cir. 1987); Lew v. Kona Hospital, 754 F.2d 1420, 1423 (9th Cir. 1985). In reviewing agency action under the Administrative Procedure Act, the Court sits not to determine facts de novo, but reviews an agency's action for error on the basis of the administrative record presented by the agency. The decision of an administrative agency "should not be reversed unless it is arbitrary, capricious, an abuse of discretion, or contrary to law." Norfolk Energy, 898 F.2d at 1439 (citing 5 U.S.C. § 706(2)(A)); Marathon Oil Co. v. United States, 807 F.2d 759, 765 (9th Cir. 1986), cert. denied, 480 U.S. 940 (1987); Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 413-14 (1971). This is a deferential standard that presumes the validity of agency actions and upholds them if they satisfy minimum standards of rationality. Ethyl Corp. v. EPA, 541 F.2d 1, 34 (D.C. Cir.) (en banc), cert. denied, 426 U.S. 941 (1976).

When a question of statutory construction is raised, federal courts must show "great deference to the interpretation given the

statute by the officers or agency charged with its administration." EPA v. National Crushed Stone Ass'n, 449 U.S. 64, 83 (1980). See Rybachek, 904 F.2d at 1284; Norfolk Energy, 898 F.2d at 1439. Even if the statute is susceptible to more than one interpretation, a court must accept the interpretation chosen by the agency if it is "reasonable." Chevron U.S.A., Inc. v. Natural Resources Defense Council, 467 U.S. 837, 844 (1984); Central Montana Elec. Power Coop. v. Administrator, Bonneville Power Admin., 840 F.2d 1472, 1476-77 (9th Cir. 1988). As explained in Chevron, "if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute." 467 U.S. at 843. See Wyckoff Co. v. EPA, 796 F.2d 1197, 1200 (9th Cir. 1986).

EPA's statutory interpretation is entitled to special deference where, as here, "the regulatory scheme is technical and complex," and EPA "considered the matter in a detailed and reasoned fashion." Chevron, 467 U.S. at 865. The court "'must look at the [agency's] decision not as the chemist, biologist or statistician that [it is] qualified neither by training nor experience to be, but as a reviewing court exercising . . . certain minimal standards of rationality.'" American Paper Inst. v. EPA, 660 F.2d 954, 963 (4th Cir. 1981) (quoting Ethyl Corp., 541 F.2d at 36).20/

20/ Courts are also particularly deferential "where the Agency's decision on the meaning or reach of the Clean Water Act involves reconciling conflicting policies committed to the Agency's care and expertise under the Act." Rybachek, 904 F.2d at 1284. See Chevron, 467 U.S. at 844.

ARGUMENT

I. TECHNOLOGY-BASED EFFLUENT LIMITATIONS WERE NOT A PREREQUISITE TO ESTABLISHMENT OF THIS TMDL.

EPA properly decided, based on the states' designation of the Columbia River as impaired due to dioxin, to establish a TMDL at this time. On appeal the Pulp Mills' sole attack on the TMDL is their argument that control measures aimed at achieving state water quality standards for dioxin in the Columbia River must be delayed until after the future development and implementation of national, technology-based effluent limitation guidelines for dioxin discharges from the pulp and paper industry. EPA interprets section 1313(d) as requiring TMDLs where existing pollution controls will not lead to attainment of water quality standards. AR No. 19(3), at 5-6, Mills ER at 132-33; 40 C.F.R. § 130.7(b). As we show below, this interpretation of the statutory scheme is reasonable whether or not existing technology-based effluent limitation guidelines specifically address dioxin. Because EPA's interpretation of its substantial statutory authority is reasonable, the Court must defer to that interpretation. Arkansas v. Oklahoma, 112 S. Ct. 1046, 1057, 1060 (1992); Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842-45 (1984).

A. The Clean Water Act Authorizes Numerous Mechanisms to Achieve State Water Quality Standards.

In adopting the Clean Water Act, Congress set a "national goal that the discharge of pollutants into the navigable waters be eliminated by 1985," and established a national policy that the discharge of toxic pollutants in toxic amounts be prohibited. 33

U.S.C. § 1251(a)(1), (3). The authority provided by specific statutory provisions must be interpreted in light of the overall goals expressed in the statute.

To achieve the Act's ambitious goals, Congress intended that both "BPT" limitations and any more stringent limitations necessary to meet water quality standards be implemented by 1977. 33 U.S.C. § 1311(b)(1). Congress also expected states to begin developing TMDLs by April, 1974.21/ On top of these requirements, Congress also directed that "BAT" limitations be achieved by 1989, and, by the same year, required states to develop ICSs for specific point sources discharging toxic pollutants to waters with impaired water quality for those pollutants. 33 U.S.C. §§ 1311(b)(2), 1314(l)(1). Congress did not specifically address how EPA should coordinate these statutory requirements to address severe pollution problems first identified long after the deadlines for the initial control actions had passed. EPA, however, has promulgated regulations that provide unequivocally that permits must contain whatever limitations are necessary to meet water quality standards, regardless of the status of development of technology-based guidelines. 40 C.F.R. § 122.44(d)(1).

As we described above, it was not until 1987 that the "Five Mill Study" confirmed that chlorine-bleaching pulp and paper mills were potential sources of dioxin contamination, and not until 1989

21/ The Act originally directed EPA to identify the pollutants suitable for daily load measurement by October, 1973, 33 U.S.C. § 1314(a)(2) (1976), and states to establish their first TMDLs within 180 days thereafter, 33 U.S.C. § 1313(d)(2) (1976). In fact, EPA published the required identification in late 1978, meaning that states' first TMDLs were due in June, 1979.

that the "104 Mill Study" confirmed that bleached kraft pulp and paper mills are a significant source of TCDD contamination in the Columbia River and its tributaries. AR No. 19(2) at 2-2, Mills ER 92; AR No. 114, SER 51-54. See also AR Nos. 124, 128. The question here is this: When new information reveals a need to control discharges of a highly toxic chemical such as dioxin, does EPA have authority to require attainment of water quality standards for that toxin without awaiting the time-consuming process of establishing, implementing, and evaluating the effectiveness of national, technology-based effluent limitation guidelines?

The Act plainly gives EPA such authority. The achievement of state water quality standards is "one of the Act's central objectives." Arkansas v. Oklahoma, 112 S. Ct. at 1056. That Congress intended water quality standards to be attained without regard to technology-based controls is evident from the structure of the Act. "Congress had a deep respect for the sanctity of water quality standards and a firm conviction of need for technology-forcing measures." Natural Resources Defense Council v. EPA, 859 F.2d 156, 208-09 (D.C. Cir. 1988). Congress granted states the authority to set their own water quality standards, and to impose stricter requirements than the nationwide minima required by the Act. 33 U.S.C. §§ 1313(c), 1370; Roosevelt Campobello Int'l Park Comm'n v. EPA, 684 F.2d 1041, 1056 (1st Cir. 1982).

> It is clear from §§ [1311] and [1370] of the Act, and the legislative history, that the states are free to force technology. . . . Only the federal effluent limitations must be technology-based, and they represent

> the minimum level of pollution reduction required by the Act. [Citation omitted.] If the states wish to achieve better water quality, they may, even at the cost of economic and social dislocations . . . .

United States Steel Corp. v. Train, 556 F.2d 822, 838 (7th Cir. 1977).

Under section 1311(b)(1)(C), EPA must include in NPDES permits whatever effluent limitations it determines are necessary to achieve state water quality standards. Trustees for Alaska v. EPA, 749 F.2d 549, 556-57 (9th Cir. 1984).[22/] On a waterway such as the Columbia which violates water quality standards because of discharges of dioxin from numerous sources, a TMDL provides a rational mechanism for deciding how much those discharges must be reduced from each source in order to achieve the applicable standards. The TMDL thus serves as a planning mechanism, which is then implemented through NPDES permit limitations, to achieve the water quality standards set by the relevant states, as required by section 1311(b)(1)(C). Those standards must be attained, even if it requires control measures more stringent than whatever technology-based standards may exist.

Moreover, Congress clearly intended TMDLs to be established on an expeditious schedule. E.g., 33 U.S.C. § 1313(d)(2) (states

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22/ See also In re City of Jacksonville, District II Wastewater Treatment Plant, NPDES Appeal No. 91-19, 1992 NPDES LEXIS 8 (EPA Envt'l Appeals Board, Aug. 4, 1992) (EPA has independent duty under section 1311(b)(1)(C) to include more stringent permit limitation when such limitation is required to meet state water quality standards); In re Star-Kist Caribe, Inc., NPDES Appeal No. 88-5, 1990 NPDES LEXIS 4 (EPA Admin'r, Apr. 16, 1990) (same). States issuing NPDES permits under section 1342(b) stand in the shoes of EPA, so that the same substantive requirements apply. Natural Resources Defense Council v. EPA, 859 F.2d 156, 183 (D.C. Cir. 1988).

to make first TMDL submission within 180 days of EPA's identification of pollutants suitable for TMDL calculation); see Scott v. City of Hammond, 741 F.2d 992, 998 (7th Cir. 1984); Environmental Defense Fund v. Costle, 657 F.2d 275, 295 (D.C. Cir. 1981).[23] If EPA and the states were required to wait until every discharger to an impaired water was covered by national technology-based standards applicable to every pollutant, see Pulp Mill Br. at 13, no TMDLs would be established for a very long time.[24] Congress plainly did not intend such delay. Section 1313(d) and EPA's implementing regulations require states to establish TMDLs when certain technology-based effluent limitations and other control measures have failed to attain water quality standards, but they neither prohibit use of TMDLs earlier nor establish TMDLs as a "last resort" to be postponed as long as possible. See 33 U.S.C. § 1313(d); 40 C.F.R. § 130.7.

Even if section 1311(b)(1)(C) and 1313(d) did not require EPA to establish the TMDL, the Act clearly authorizes it. Section 1342(a)(1) expressly authorizes EPA to require "such [permit] conditions as [EPA] determines are necessary to carry out the

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[23] As we have shown, this TMDL was promulgated in conjunction with the establishment of ICSs for the Pulp Mills pursuant to the requirements of section 1314(l). The similarly short deadlines in that section clearly do not contemplate a delay in applying limitations in order to await development of technology-based standards.

[24] See 58 Fed. Reg. 66,078 (Dec. 17, 1993) (nationwide effluent guidelines for BAT relating to dioxin discharges from pulp mills proposed in late 1993). See Natural Resources Defense Council v. Reilly, 32 Env't Rep. Cas. (BNA) 1969, 1973 (D.D.C. 1991) (referring to the "ponderousness and enormity of the agency's task" in establishing effluent limitations guidelines); Chemical Mfrs. Ass'n v. Natural Resources Defense Council, 470 U.S. 116, 132 & n.24 (1985).

provisions of [the Act]," prior to taking actions necessary to implement the requirements of 33 U.S.C. §§ 1311, 1312, 1316, 1317, 1318, and 1343. Here, EPA has determined that the WLAs established by the TMDL are necessary to carry out the provisions of the Act -- specifically sections 1251(a)(3), 1311(b)(1)(C), 1313(c), 1313(d) and 1314(l) -- prior to taking the regulatory actions necessary to establish nationwide technology-based effluent limitations for dioxin. See Trustees for Alaska, 749 F.2d at 558. Thus, the TMDL is authorized by EPA's broad discretion under section 1342(a)(1) without regard to whether technology-based limitations for dioxin have been established or would lead to future attainment of water quality standards.25/

In light of this broad statutory authority to achieve water quality standards, EPA interpreted section 1313(d) as authorizing the Columbia River TMDL where the applicable standards for dioxin had not been achieved by the existing effluent limitations in the Pulp Mills' NPDES permits, even though the existing permits did not contain a specific technology-based, numeric limitation on dioxin discharges. AR No. 19(3), at 5-6, Mills ER at 132-33. EPA reasoned that if technology-based limits developed in the future, based either on national effluent limitation guidelines or on a BPJ basis, are more stringent than the wasteload allocations established as part of the TMDL, those stricter limits will have to be complied with, and the WLAs will have no practical effect.

25/ Cf. Arkansas v. Oklahoma, 112 S. Ct. at 1056 (Congress has vested in EPA "broad discretion" to establish conditions for NPDES permits, and to oversee state permit programs); id. at 1058 (the Act grants EPA and the states "broad authority" to develop area-wide programs to alleviate and eliminate existing pollution).

AR No. 19(3) at 5, Mills ER at 132. But if future technology-based limits are less stringent, then the water quality-based allocations in the TMDL will continue to be necessary to satisfy the requirements of the Act, and there is no valid reason to allow continued violation of the water quality standards in the interim. See id. This interpretation of the statutory scheme is reasonable, and must therefore be upheld.

Finally, the Pulp Mills' argument that the TMDL disadvantages the pulp and paper mills of the Pacific Northwest as against their rivals in other regions, Pulp Mill Br. at 12, is a red herring. The Act gives states primary authority to establish water quality standards, and those standards may vary across the country, because states may set more stringent water quality standards than the minimum protections required by the Act.[26/] If the Pulp Mills have a complaint about the applicable water quality standards in Washington, Oregon and Idaho, they should petition the states for a modification of those standards.

B. Even If Technology-Based Controls Were Required Before Establishment of TMDLs, That Language Refers to BPT Controls, Not BAT Controls.

Even if the Pulp Mills were correct that a TMDL may be established only after pollutant-specific, national technology-based effluent limitations have been incorporated in their permits and have failed to achieve water quality standards, their suggestion that BAT limits must first be applied, see Pulp Mill

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26/ States may establish their own water quality standards provided that EPA approves them as scientifically defensible and generally consistent with the requirements of the Act. 40 C.F.R. Part 131.

Br. at 15, 17-18, is plainly erroneous.[27] Sections 1313(d)(1)(A) & (C) direct states to establish TMDLs where effluent limitations required by sections 1311(b)(1)(A) and (B) are not adequate to implement water quality standards. In turn, those sections require effluent limitations consistent with application of "best practicable control technology currently available" ("BPT" limitations) for industrial point sources, and "secondary treatment" for publicly owned treatment works.[28] Section 1313(d) does not mention BAT limitations.

The Pulp Mills would supplement the plain language of section 1313(d) by requiring EPA to consider whether future application of nationwide BAT limitations for toxic pollutants might also lead to attainment of water quality standards. Pulp Mill Br. at 13-18.[29] BAT, or "best available technology economically achievable" limitations, are developed under sections 1311(b)(2)(A) and

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[27] In comments submitted to the Agency, the Pulp Mills argued that BAT limitations must be applied before a TMDL can be established. See AR No. 49, at 2 (Preliminary Comments of Weyerhaeuser); AR No. 90, at 13, 18 (Comments of Longview Fibre); AR No. 19(3) at 5, Mills ER at 132. In their brief here, the Mills attempt to blur the distinction between BPT and BAT limitations, but it is apparent that their goal is to delay implementation of a TMDL until after BAT limits are established. See Pulp Mill Br. at 17-18. Moreover, the Pulp Mills are limited here to arguments they presented to the Agency in a meaningful way in the first instance. See Vermont Yankee Nuclear Power Corp. v. Natural Resources Defense Council, 435 U.S. 519, 553-54 (1978). Thus, we do not understand the Mills to be suggesting here that EPA should establish BPT limits for dioxin discharges from pulp mills, rather than the more stringent BAT limits required by 33 U.S.C. § 1311(b)(2).

[28] See Homestake Mining Co. v. EPA, 595 F.2d 421, 427 (8th Cir. 1979).

[29] The Pulp Mills refer to EPA's schedule for developing BAT effluent limitations guidelines, which contemplates establishment of such guidelines for pulp mill discharges of dioxin in 1995. Id. at 17 & n.13.

1314(b)(2)(A), and are not mentioned in section 1313(d). There is no basis in the statutory language for the Mills' proposed additional constraint on EPA's TMDL authority.30/ Moreover, when Congress adopted the TMDL provisions in 1972, it expected states to establish TMDLs long before BAT limitations were in place. Congress initially intended that BAT effluent limitations be attained by July, 1983. 33 U.S.C. § 1311(b)(2)(A) (1976). In contrast, Congress expected states to begin developing TMDLs by April, 1974, well before Congress expected BAT effluent limitation guidelines to be in place. See supra at 23.

C. The Pulp Mills Are Already Subject to Technology-Based Limitations.

The Pulp Mills' challenge to EPA's TMDL authority must also fail because the Mills are already subject to technology-based effluent limitations in their permits, and those limitations have not been adequate to attain all applicable water quality standards. EPA has promulgated nationally-applicable BPT and BAT limitations for discharges of a number of pollutants by members of the pulp and paper industry. 40 C.F.R. Part 430. These guidelines, implemented through NPDES permits, have been inadequate to provide for attainment of the water quality standards for dioxin

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30/ EPA regulations provide that TMDLs are not required under section 1313(d)(1) where various pollution control measures other than BPT and secondary treatment limitations are in place and are sufficient to implement water quality standards. See 40 C.F.R. § 130.7(b). That regulation does not require EPA or the states to adopt such other controls before exercising TMDL authority. In construing administrative regulations, courts must give "controlling weight" to the agency's interpretation, "unless it is plainly erroneous or inconsistent with the regulation." United States v. Larionoff, 431 U.S. 864, 872 (1977); Nevada Land, 8 F.3d at 717; Norfolk Energy, 898 F.2d at 1439.

in the Columbia River. Since these guidelines do not specifically address dioxin, it is clear that BPT and BAT limitations based on the national guidelines are inadequate to remedy waters impaired due to dioxin discharges. Thus, even if establishment of national BPT and BAT limitation guidelines were a prerequisite to TMDL development, that prerequisite has been established here.

In addition, every discharger is already covered by technology-based limits determined by the best professional judgment ("BPJ") of permit writers. Natural Resources Defense Council v. EPA, 859 F.2d 156, 183, 185 (D.C. Cir. 1988) (citing section 1342(a)(1)); Natural Resources Defense Council v. Reilly, 32 Env't Rep. Cas. (BNA) 1969, 1975 (D.D.C. 1991); see AR No. 19(3) at 4, Mills ER at 131. These existing BPJ limitations (which do not specifically address dioxin) have also been inadequate to ensure that the Pulp Mills' discharges comply with the water quality standards for dioxin. See AR No. 19(3) at 5, Mills ER at 132.

As EPA noted in establishing the TMDL, it is not reasonable to assume that future BAT limitations based on any revised national guidelines will result in attainment of water quality standards for dioxin in the Columbia River. AR No. 19(3) at 5, Mills ER at 132. Indulging in such an assumption could lead to the water quality standards being violated for another five years, plus further delays while additional controls are implemented. Id. EPA believed that such delay in imposing effective controls on such a highly toxic pollutant would be "contrary to the very essence" of section 1313(d). Id. Thus, EPA reasonably determined that establishment of the TMDL need not be delayed until after the

implementation of BAT limitations on discharges of dioxin, and the district court properly entered summary judgment in favor of EPA on the Pulp Mills' complaint.

II. EPA'S DECISION TO BASE THE TMDL ON TCDD ALONE WAS NOT ARBITRARY OR CAPRICIOUS.

EPA established its TMDL for 2,3,7,8-TCDD -- the toxic pollutant identified by the states under section 1313(d)(1)(A) as impairing the water quality of the Columbia River, and for which ICSs under section 1314(l) were required on an expeditious time schedule. DOC challenges EPA's decision to address only TCDD in this TMDL, DOC Br. at 11-14, 32-33, but fails to provide a single citation to any provision of the Clean Water Act in support of its position that a TMDL must address all pollutants in a single analysis. DOC completely ignores the rationale provided by the Agency for focussing on TCDD alone, and instead asks this Court to override EPA's reasoned determination on the proper scope of its TMDL.

A. The Clean Water Act Does Not Preclude EPA from Establishing Pollutant-Specific TMDLs.

DOC claims that EPA's TMDL is arbitrary and capricious because it establishes TCDD loadings without accounting for the presence in the Columbia River of a number of pollutants other than TCDD that may also be impairing water quality. DOC claims EPA was also required to consider the presence of an unidentified number of PCBs, PCCs, naphthalenes, and other related chemicals when determining loading limits for TCDD. DOC Br. at 11-12.

Essentially DOC argues that all water quality impairments must be addressed in a single TMDL. These arguments have no merit.31/

Nothing in the Clean Water Act or EPA regulations suggests that a single TMDL must address all pollution problems in a waterbody. Indeed, in the preamble to its regulations implementing section 1313(d), EPA explained that:

> [A] single TMDL covers only one specific pollutant or one property of pollution, for example acidity, biochemical oxygen demand, radioactivity or toxicity. Thus, more than one TMDL may be required for a segment where there may be violations of more than one criterion in the applicable [water quality standard].

50 Fed. Reg. 1,774, 1,776 (Jan. 11, 1985). Thus, EPA interprets the Act as allowing multiple TMDLs where there are multiple pollutants or pollutant properties causing impairments in a given waterbody.

EPA's interpretation of the proper scope of a TMDL is consistent with the Act's mandate that TMDLs be developed on a priority basis. Section 1313(d)(1)(C) requires that TMDLs be developed in accordance with a priority ranking of impaired waters established by the states pursuant to section 1313(d)(1)(A). As the district court found, the Act's prioritized approach to the worst pollution problems would be hampered if all impairments in a waterbody were required to be addressed in a single TMDL. CR No.

31/ DOC's arguments also ignore the fact that limitations required to meet water quality standards must be included in NPDES permits issued under section 1342 of the Act, whether or not TMDLs have been established. 33 U.S.C. §§ 1311(b)(1)(A) & (C), 1342(a)(1); 40 C.F.R. §§ 122.44(b)(1), 122.44(d)(1). Trustees for Alaska, 749 F.2d at 556-57. Thus, there is no valid reason based on environmental or human health concerns to require that EPA's TMDL address all of the possible water quality problems in the Columbia River.

88 at 17, Mills ER 248. Rather, the states and EPA must be allowed to address the worst problems in various waters first, retaining the ability to perform additional TMDLs for these waters and for other pollutants at a later date.

Thus, the Act does not require that EPA's TMDL for TCDD also cover the host of chemicals which DOC now alleges to be of concern in the Columbia River. Separate TMDLs can be prepared for these various chemicals if and when it is determined that they are causing an impairment in the Columbia River, either singly or as a group. Accordingly, if DOC believes that a toxic mixture of chemicals is present in the Columbia River notwithstanding implementation of the TMDL for TCDD, it should present its evidence to the states of Oregon, Washington and Idaho and request that they list the Columbia River under section 1313(d)(1)(A) as impaired due to the presence of these mixtures and identify development of a TMDL for them as a high priority.[32/] DOC should not be allowed to circumvent this statutorily-prescribed listing and prioritization process through an end-run against EPA's TMDL for dioxin.[33/]

32/ The States are required to update and revise their section 1313(d) lists of impaired waters and their priority ranking of waters for TMDL development every two years. 40 C.F.R. § 130.7(d)(1).

33/ Cf. Hazardous Waste Treatment Council v. EPA, 861 F.2d 277, 287 (D.C. Cir. 1988), cert. denied, 490 U.S. 1106 (1989) ("[A]n agency's failure to regulate more comprehensively is not ordinarily a basis for concluding that the regulations already promulgated are invalid.").

B. EPA Had Good Reasons to Limit the Scope of its TMDL to TCDD.

EPA considered establishing the TMDL to account for the presence of all chlorinated dibenzo-p-dioxins ("CDDs") and chlorinated dibenzo-furans ("CDFs") in the river, and explained a number of reasons why it did not do so. AR No. 19(3) at 25-26, Mills ER 152-53. For example, EPA explained that since TCDD is the most toxic of these compounds, its control would greatly reduce the risk posed by dioxins and furans in general.34/ EPA also explained that there was as yet inadequate information available to determine the degree to which CDDs and CDFs other than TCDD can be expected to persist in the environment and bioconcentrate in fish. Such considerations are of critical importance in establishing numeric interpretations of narrative criteria.

Since establishing the TMDL for TCDD, EPA has conducted research on the environmental fate of CDDs and CDFs, and has solicited comment on a protocol for equating their relative properties in this regard to the properties of TCDD.35/ EPA's

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34/ As one of the 65 toxic pollutants identified for heightened attention under section 1317(a) of the Act, TCDD is the only CDD or CDF for which Congress mandated that individual control strategies be developed. 33 U.S.C. § 1314(l)(1)(D); 40 C.F.R. § 401.15; see Natural Resources Defense Council v. EPA, 915 F.2d at 1316 n.1. EPA noted in its TMDL Decision Document that the TMDL would be used by the states in developing these ICSs. AR No. 19(2) at 2-1, Mills ER 91. Thus, the state and EPA prioritization of TCDD for TMDL development reflects a priority for action established directly by Congress.

35/ EPA derived "bioaccumulation equivalency factors" ("BEFs") for CDDs and CDFs as part of its proposed water quality standards guidance for the Great Lakes developed pursuant to 33 U.S.C. § 1268(c)(2). 58 Fed. Reg. 20,802, 20,943 (April 16, 1993). The (continued...)

TMDL decision allowed it to move forward with controls on TCDD while developing the technical capacity for doing more, if needed. The alternative, apparently preferred by DOC, would have involved lengthy delay in regulating TCDD while EPA developed a protocol for evaluating the environmental fate of other CDDs and CDFs.

EPA also explained that with respect to protection of human health from carcinogenic effects, the states bordering the Columbia River regulated pollutants on a chemical-by-chemical basis such that no one chemical would cause more than one additional cancer per one million people exposed. AR No. 19(3) at 26, Mills ER 153. EPA views decisions regarding tolerable cancer risk of pollutants in surface waters to be primarily a risk management decision of the states. 57 Fed. Reg. 60,864. The states' chemical-by-chemical approach to regulating carcinogens supported EPA's single-pollutant approach to establishing the TMDL.

As the district court held, EPA rationally chose to pursue regulation of dioxin as the most toxic of those chemicals threatening the Columbia River. CR No. 88 at 18, Mills ER 249. The Agency's judgment was based on complex scientific determinations and technical expertise, and is entitled to deference. See Hercules, Inc. v. EPA, 598 F.2d 91, 106 (D.C. Cir. 1978).

III. EPA REASONABLY SELECTED 0.013 PPQ AS AN AMBIENT TCDD CONCENTRATION PROTECTIVE OF HUMAN HEALTH.

By imposing dioxin allocations set at the very limit of detection capabilities, EPA's TMDL will reduce pulp mill

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35/ (...continued)
proposed BEFs vary between 0.003 and 1.8, indicating that the bioaccumulation potential of the various CDDs and CDFs studied ranges from three one-thousandths to roughly twice that of TCDD.

discharges of dioxin by approximately 95 percent. See AR Nos. 19(1), 19(2) at 3-9 and C-2 to -3, Mills ER 84, 102, 124-25. Nonetheless, DOC argues that these control measures -- the most stringent in the nation -- should be overturned as inadequate to protect the health of Native Americans and other populations that consume more fish than is found in an average diet. While EPA is committed to gathering and evaluating additional data on consumption of Columbia River fish, the record before the Agency at the time it acted establishes that the TMDL is sufficiently stringent to protect the health of all persons living in the Columbia River basin, including those with diets high in fish.

A. EPA Is Continuing to Collect and Analyze Data on Fish Consumption Patterns.

At the time EPA established the TMDL in 1991, it had before it a draft report by two EPA scientists discussing the possible risk to human populations in the Columbia River basin from consumption of fish caught near pulp mills, on which DOC relies here, AR No. 121, and a study commissioned by the Pulp Mills showing much lower estimates of fish consumption rates by Native Americans and other exposed populations, see AR No. 116. While EPA acted reasonably in establishing the TMDL based on the record before it, the Agency noted that "follow-up work is in progress." AR No. 19(3) at 10, Mills ER 137. Since that time, EPA has commissioned a more detailed study by the Columbia River Intertribal Fish Commission ("CRITFC") of fish consumption patterns among Native Americans in the Columbia River basin. The first phase of that study, nearly completed, has collected data on the amount of fish from the Columbia River consumed by Native Americans in the area.

On February 11, 1994, President Clinton signed Executive Order 12898, regarding federal actions to address environmental justice concerns in minority and low income populations. 59 Fed. Reg. 7,629 (Feb. 16, 1994). Among other things, that order directs federal agencies to collect and analyze information on consumption patterns of populations who principally rely on fish and/or wildlife for subsistence, and to develop guidance for the evaluation of human health risks associated with the consumption of pollutant-bearing fish or wildlife. Id. § 4-4.[36/] Consistent with the Executive Order, EPA has recently decided to move forward with a second phase of the CRITFC study, to assess the concentrations of dioxin found in the specific types of fish that make up the diet of Native Americans in the Columbia River basin. If the new studies suggest that the current state water quality standards for the Columbia River are not sufficiently protective of the health of Native Americans, one appropriate avenue for seeking revisions is through the states' triennial review of their water quality standards. See 33 U.S.C. § 1313(c)(1); AR No. 19(3) at 10, Mills ER 137. Of course, any change in the applicable numeric water quality standards would warrant consideration of whether a new TMDL is necessary to implement the revised standards.

B. On the Basis of the Administrative Record Before It, EPA Acted Reasonably in Establishing the TMDL to Achieve Existing State Water Quality Standards.

As we have shown, EPA's calculation of wasteload allocations for the Pulp Mills was influenced by the analytical detection

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[36/] The order does not create any judicially-enforceable rights, id. § 6-609, and cannot in any event affect the legal validity of agency action taken three years earlier.

limit for dioxin. AR No. 10(2) at 19, Mills ER 23; see supra at 14. As EPA explained, a permit condition set at a level below the general analytical detection limit would make it difficult or impossible to measure compliance. AR No. 10(2) at 20, Mills ER 24. See also AR No. 19(2) at 3-9, Mills ER 102.

EPA searched for creative approaches to reduce the dioxin loading from pulp mills even further than could be achieved by monitoring concentrations in total plant effluent. Because dioxin concentrations are higher in bleach plant flow than in total plant effluent, EPA determined that wasteload allocations which result in total plant effluent concentration limits even below the analytical detection limit could be monitored for compliance if monitoring were moved upstream in the mill to the bleach plant. AR No. 19(2) at C-2, Mills ER 124. In addition, EPA determined statistically that it could reduce total dioxin loading to the river still further by setting a maximum concentration at the 10 ppq detection limit, rather than using a long term average of 10 ppq. AR No. 19(2) at C-2 to C-3, Mills ER 124-25. Thus, EPA established the most stringent wasteload allocations for the Pulp Mills that it could monitor using existing analytical detection capabilities.

1. EPA Interpreted the States' Narrative Criteria Consistent With EPA's Technical Dioxin Guidance.

Although EPA is continuing to gather fish consumption data in the Columbia River basin, the administrative record demonstrates that EPA's interpretation of the state narrative dioxin criteria was sensible and protective based on the information available to the Agency at the time it acted. Fish consumption estimates are

just one factor in an equation used to estimate health risk, and EPA made generally conservative (i.e., protective) assumptions with respect to the other factors. Even assuming the higher fish consumption levels cited by DOC, the TMDL provides protection for Native Americans and other populations that is well within the cancer risk range that EPA has found to be adequately protective.

At the time the Columbia River TMDL was established, only Oregon had a numeric water quality criterion for dioxin, and it addressed human health concerns only. Accordingly, EPA interpreted the narrative criteria in Washington and Idaho to derive an ambient TCDD concentration protective of human health for Columbia River waters within those states.[37/] For reasons articulated in EPA's TMDL Decision Document, EPA interpreted the narrative water quality criteria in Washington and Idaho to be consistent with Oregon's numeric standard.[38/] EPA explained that the 0.013 ppq value it selected to implement narrative criteria in Washington and Idaho was based on the assumptions and analyses in EPA's Dioxin Criteria Document, AR No. 107. See AR No. 19(2) at 2-2, Mills ER 92. This 300-page analysis provides a comprehensive summary of information relevant to deriving a human health criterion, and suggests various criterion values -- including the 0.013 ppq value used as a basis for the Columbia River TMDL --

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37/ The narrative criteria provide generally that toxic substances may not be introduced in concentrations that may adversely affect public health or designated uses of the waters. See AR No. 10(2) at 7, Mills ER 11.

38/ EPA also interpreted the state narrative criteria as necessary to protect aquatic life and wildlife. See Part IV, infra.

that would protect human health with varying degrees of risk. AR No. 107 at C-181, SER 43.

DOC claims that the TMDL should have been based on attaining a lower ambient level of dioxin than 0.013 ppq. Specifically, it argues that the 0.013 ppq value was derived by assuming a fish consumption rate of 6.5 grams per day, and that the criterion will not protect those residents of the Columbia River Basin who eat 150 grams per day of fish. DOC Br. at 10, 29-31. Contrary to DOC's assertions, EPA's interpretation of the states' narrative criteria was reasonable, and is entitled to deference.[39/]

2. Scientific Background for Derivation of a Dioxin Water Quality Criterion

A numeric water quality criterion to protect human health from the presence of a chemical such as dioxin in surface waters is based on three fundamental considerations: (1) an assessment of the degree or probability of harm associated with varying doses of the chemical, (2) an estimate of the dose to humans that is likely to result from varying concentrations of the chemical in surface waters, and (3) a decision regarding the degree of risk to human health that is tolerable. See AR No. 107.

To determine the probability of adverse human health effects as a result of exposure to varying doses of dioxin, EPA calculated a "potency factor" for dioxin that is the most stringent of any

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39/ Since establishment of the TMDL, EPA has promulgated numeric human health dioxin criteria of 0.013 ppq for Idaho and Washington. 57 Fed. Reg. 60,922-23. Thus, all states in the Columbia River basin have now incorporated a numeric 0.013 ppq TCDD criterion into their water quality standards.

used by any regulatory agency in the world.[40/] AR No. 116 at 19a, SER 56. All else being equal, use of the potency factors or "safe" dioxin levels calculated by other federal agencies or foreign governments would result in a criterion from five to sixteen hundred times less stringent than EPA's 0.013 ppq value. Id.

The second step in calculating a numeric dioxin water quality criterion involves estimating the dose of dioxin to humans that is likely to result from its presence in surface waters. There are two primary human routes of exposure: drinking the water, and eating fish and shellfish. Because of the tendency of dioxin to concentrate in fish tissues at levels thousands of times greater than in the ambient water, the fish consumption exposure route is by far the most significant. AR No. 107 at C-181, SER 43.

EPA has calculated a "bioconcentration factor" ("BCF") of 5,000 that can be used to estimate dioxin concentration in fish as a multiple of the chemical's concentration in surface water. AR No. 107 at B-3 to B-10, C-179, SER 22-29, 41. With this tool for estimating fish tissue residues, the next step in estimating the potential dose to humans as a result of the presence of dioxin in surface water is to derive an estimate of the amount of pollutant-bearing fish likely to be consumed. As described in more detail

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40/ The EPA potency factor is expressed mathematically as 1.56×10^{-4} for every picogram (one trillionth of a gram) per kilogram per day of dioxin exposure. AR No. 107 at C-243, SER 49. In other words, the EPA potency factor estimates that an upper bound of 1.56 out of every 10,000 people who are exposed to a dose of one picogram per kilogram per day will develop cancer over a lifetime of exposure.

below, EPA used a value of 6.5 grams per day for this purpose.[41] AR No. 107 at C-181, C-183, SER 43, 45.

The last major consideration in deriving a criterion is an assessment of the degree of risk that should be deemed tolerable. EPA's 0.013 ppq dioxin criterion is based on a plausible upper bound one-in-one-million risk of developing cancer over a lifetime of exposure. AR No. 107 at C-181, SER 43. This risk level is in the more protective range of risk levels that EPA has used or approved in state and federal regulatory actions. See, e.g., 57 Fed. Reg. 60,848, 60,864 (EPA promulgation of water quality criteria for states using either a one-in-one million or a one-in-one-hundred-thousand risk level, depending on state policies.) All else being equal, use of the one-in-a-million target risk level yields criteria ten times more stringent than those criteria that are based on a risk level of one-in-one-hundred-thousand. Id.[42]

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[41] Assuming that a waterbody has ambient dioxin concentrations of 0.013 ppq (0.013 picograms per liter), the dioxin expected in fish flesh would be equal to that ambient concentration times the BCF of 5,000, or 65 picograms of dioxin per kilogram of fish. Assuming consumption of 6.5 grams (0.0065 kilograms) per day of such fish, the total dioxin ingested per day as a result of fish consumption would be 0.4225 picograms of dioxin.

[42] EPA combines the various risk assessment factors described above in the following formula to derive a numeric dioxin water quality criterion for protection of human health:

$$\text{CRITERION} = \frac{\text{RISK LEVEL X BODY WEIGHT}}{\text{POTENCY X ((WATER INTAKE) + (FISH CONSUMPTION X BCF))}}$$

Derivation of this formula is discussed generally at 45 Fed. Reg. 79,353, col. 1 (Nov. 28, 1980).

3. The 6.5 Gram Per Day Value Is Intended to Represent Only a Subset of Total Fish Consumption.

As described above, pollutant-bearing fish consumption rates are considered in setting water quality criteria because consumption of pollutant-bearing fish is a major pathway for human exposure to pollutants present in surface waters. Of course, fish consumption is only a concern to the extent that fish contain pollutant residues. The fish consumption rate is used in the criteria derivation formula to account for consumption of pollutant-bearing fish. Thus, all of the fish in the estimate are assumed to include a level of dioxin determined by the maximum level in ambient water (0.013 ppq here) and the dioxin bioconcentration factor (5,000), or 0.065 parts per trillion.[43/] In other words, all of the fish covered by the fish consumption rate are assumed to have the maximum residues of dioxin permitted by the water quality criterion. See 57 Fed. Reg. 60,848, 60,863, col. 1.

Actual consumption rates of such maximum residue fish are likely to vary from one waterbody to another, depending on such factors as the presence of anadromous fish (i.e., fish that live their adult lives in the ocean and only enter rivers in order to spawn). For purposes of deriving numeric water quality criteria, EPA made a reasonable assumption that the consumption rates of such maximum residue fish would be equal to the national average total consumption rate for all (pollutant-bearing and non pollutant-bearing) freshwater and estuarine fish, or 6.5 grams per day. 45 Fed. Reg. 79,348, col. 3 (Nov. 28, 1980).

43/ EPA rounded this value up to 0.07 parts per trillion in describing its final TMDL. AR No. 19(2) at 2-2, Mills ER 92.

DOC notes that some individuals in the Columbia River area consume 150 grams per day of fish. However, nothing in the administrative record suggests that those individuals will, after implementation of the TMDL, ingest more dioxin than they would by consuming 6.5 grams per day of maximum residue fish. Indeed, due to the large runs of anadromous fish on the Columbia River, see AR No. 116 at 30-31, SER 57-58, there is likely to be a significant difference between the total fish consumption rate and the rate of consumption of pollutant-bearing fish only. Anadromous fish such as salmon that frequent the Columbia River spend their adult lives in the oceans far from sources of dioxin discharge and would not be expected to bioconcentrate dioxin to any considerable degree during their brief stay in the Columbia River to spawn. AR No. 51(4) at 2, SER 11.

Thus, the total fish consumption rate of various individuals is not determinative; the central question is whether the actual rate of ingestion of dioxin is greater than that assumed by EPA. In Natural Resources Defense Council v. EPA, 16 F.3d 1395, 37 Env't Rep. Cas. (BNA) 1953 (4th Cir. 1993), use of a 6.5 gram per day fish consumption rate was challenged in the context of EPA approval of dioxin criteria adopted by the states of Maryland and Virginia. There, too, plaintiffs alleged that certain individuals consumed more than a total of 6.5 grams per day of fish. 37 Env't Rep. Cas. at 1958. The court, however, recognized that the 6.5 gram per day value is premised upon the subset of fish that contain the maximum residues of dioxin permissible under state law, id. at 1959, and held that EPA had relied on a scientifically

defensible means to reach reasoned judgments concerning fish consumption levels. Id. Accordingly, the court upheld EPA's approval of the criteria. Id. at 1963.44/ Similarly here, DOC has failed to overcome the presumption of validity accorded to EPA's TMDL. See Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 419 (1971); Ethyl Corp v. EPA, 541 F.2d at 34; Mt. Airy Ref. Co. v. Schlesinger, 481 F. Supp. 257, 264 (D.D.C. 1979).

As shown above, the 0.013 ppq value is designed to provide protection to the one-in-a-million risk level assuming consumption of maximum residue fish at the rate of 6.5 grams per day. Even assuming arguendo that the individuals DOC has described who eat 150 grams per day of fish are eating exclusively maximum residue fish, 23 times the value assumed by EPA, those individuals would bear a dioxin risk of 23 in a million. EPA has historically set health-based standards at risk levels between one-in-a-million (10^{-6}) and one-hundred-in-a-million (10^{-4}), and courts have upheld such levels as adequately protective of human health. See Ohio v. EPA, 997 F.2d 1520, 1533 (D.C. Cir. 1993); CR No. 88 at 16-17 n.5, Mills ER 247-48 n.5. See also, 56 Fed. Reg. 33,050, 33,081 (July 18, 1991); 57 Fed. Reg. 60,848, 60,864 (Dec. 22, 1992). Moreover, if individuals in the Columbia River basin are exposed to an increased cancer risk of 23 in a million, they would still be

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44/ It is noteworthy that the state numeric criteria at issue in NRDC were established at 1.2 ppq, see id. at 1958 -- approximately one hundred times less stringent than the 0.013 ppq standard that the Columbia River TMDL is designed to achieve. Notwithstanding an attack on virtually every component of the risk assessment used by the states to derive these criteria, the court upheld EPA's approval of the criteria as protective of human health. Id. at 1963.

subject to four times less risk than an average resident of Virginia or Maryland, where the Fourth Circuit has upheld EPA's approval of water quality standards for dioxin that are approximately 100 times less stringent.

C. DOC's Attacks on the TMDL Are Based on Misleading and Erroneous Characterizations of the Record and the Applicable State Water Quality Standards.

DOC's contention that the TMDL subjects certain populations to risk levels of 8,600 in a million, DOC Br. at 10-11, 30-31, is based on a simple misunderstanding or mischaracterization of the record. The hypothetical discussion of possible risk on which DOC relies, AR No. 121, was prepared before the TMDL was established, and it analyzed the risk to Native Americans, Asians and subsistence fishermen living in the Columbia River basin in the absence of the TMDL. It thus supported the need to address dioxin contamination in the Columbia River and the establishment of a TMDL. That draft analysis assumed a maximum dioxin concentration of 24 picograms per gram -- or 24,000 picograms per kilogram -- in the tissues of fish consumed. DOC ER Tab 47, AR No. 121, at 3. As we explained above, supra at 43 n.41, implementation of the TMDL is expected to result in maximum dioxin concentrations in fish tissue of only 65 picograms per kilogram, resulting in risk figures approximately three orders of magnitude smaller than those claimed by DOC. Thus, DOC is simply in error in claiming that EPA calculated post-TMDL risk levels in excess of those relied upon by the district court. See DOC Br. at 31; Mills ER 247-48 & n.5.

DOC's argument is also misleading in suggesting that the states of Washington, Oregon and Idaho have selected a one per

million risk level as the applicable water quality standard to be achieved by the TMDL. DOC Br. at 31. As shown above, supra at 41-43 & n.42, the designated risk level is merely one factor included in the equation for calculating a numeric water quality standard. The risk level is applied together with certain reasonable assumptions, such as fish and water consumption rates, bioconcentration factor, and so on, in order to arrive at a numeric criterion.45/ The risk level chosen by a state is not part of the state's narrative criteria, nor is it a freestanding "standard" to be applied to the particularized exposure levels of specific individuals or sub-populations. Rather, states' choice of a highly protective risk level already reflects consideration of the fact that some people invariably have higher exposure to certain risks than others. In other words, states may choose to provide a high level of protection for the average population in order to provide what they deem adequate protection for more sensitive populations.46/ There is no basis for DOC's suggestion that the use by Washington, Oregon and Idaho of a one per million risk level as one of several factors used to establish numerical

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45/ See, e.g., 57 Fed. Reg. at 60,863 (detailing assumptions used in deriving criteria, and indicating that "individuals that ingest ten times more of a pollutant than is assumed in derivation of the criteria at a 10^{-6} risk level will be protected to a 10^{-5} level, which EPA has historically considered to be adequately protective.").

46/ See, id. (referring to EPA's "focus on promulgation of appropriate State-wide criteria that will reduce risks to all exposed individuals, including highly exposed subpopulations.").

criteria requires that every individual be protected to at least a one per million risk level.47/

In sum, EPA's TMDL provides adequate protection for all residents of the Columbia River basin, and EPA will continue to gather additional data on fish consumption patterns. Based on the administrative record compiled by EPA in devising the TMDL, the TMDL is protective of human health, and implements all state numeric and narrative water quality standards. Therefore, the district court properly granted EPA's motion for summary judgment.

IV. THE TMDL WILL IMPLEMENT STATE WATER QUALITY STANDARDS FOR THE PROTECTION OF AQUATIC LIFE AND WILDLIFE.

DOC's final claim is based on the contention that EPA failed to consider the possible effects of dioxin on aquatic life and wildlife, and therefore failed to implement all applicable water quality standards for dioxin as required under section 1313(d). DOC Br. at 6, 18-20. This is simply wrong. Although the Columbia River was identified as being water quality impaired as a result of exceeding the 0.013 ppq human health criterion, AR No. 19(2) at 2-2 to 2-3, Mills ER 92-93, EPA was mindful of the toxic effects of dioxin on aquatic life and wildlife as well, see AR No. 107, and took them into account in deriving the TMDL.

Richard Albright, the Chief of the Water Quality Section in EPA's Regional Office in Seattle, and one of three EPA officials primarily responsible for development of the Columbia River TMDL, explained in a declaration accepted by the district court, CR No.

47/ DOC's strained argument would also establish as state water quality "standards" other factors in the criterion derivation formula, such as the consumption of 6.5 grams per day of fish, or a human life span of 70 years.

47 Exh. C, SER 64, that EPA did not limit its consideration to human health effects. On the contrary, "the TMDL was intended and designed to provide protection to humans, aquatic life, and wildlife." Id. at 3, SER 66. Mr. Albright determined, based on a review of record materials, that the 0.013 ppq human health criterion would also be broadly protective of aquatic life and wildlife. Id. at 2-3, SER 65-66.

The record supports this conclusion. First, a 1986 Biological Report issued by the USFWS (the "USFWS Dioxin Hazard Document") provides that "2,3,7,8-TCDD concentrations in water should not exceed 0.01 ppt [part per trillion] to protect aquatic life, or 10 to 12 ppt in food items of birds and other wildlife." AR No. 142, at iii, SER 60. The 0.013 ppq ambient concentration set by the TMDL is one one-thousandth of the 0.01 ppt ambient value that the USFWS Dioxin Hazard Document indicates is protective of aquatic life.48/ The TMDL is designed to yield maximum fish tissue residues of 0.07 ppt in fish. AR No. 19(2) at 2-2, Mills ER 92. This is roughly one hundred fortieth to one

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48/ The effects of dioxin on aquatic life are also discussed in EPA's dioxin criteria guidance document. AR No. 107, at B-1 through B-18, SER 20-37. The document reports that the lowest dioxin concentration at which adverse effects to aquatic animal life were observed was 0.0001 micrograms per liter (100 ppq). See AR No. 107 at B-7, SER 26. The 0.013 ppq goal of the TMDL is approximately one ten-thousandth of this value. Also, dioxin was not found to cause adverse effects to aquatic plants exposed to dioxin at concentrations up to 1.3 micrograms per liter. Id. at B-3, SER 22. The TMDL will attain an ambient dioxin concentration that is one hundred million times less than this value. Thus, contrary to DOC's assertions, DOC Br. at 21, this document certainly supports EPA's finding that the TMDL will protect aquatic life.

hundred seventieth of the USFWS' recommended value for the protection of birds and other wildlife.

Second, EPA's Background Document to the Integrated Risk Assessment for Dioxins and Furans from Chlorine Bleaching in Pulp and Paper Mills provides further confirmation that the TMDL will protect wildlife. Using a somewhat more conservative analysis than the USFWS Dioxin Hazard Document, it indicates that adverse effects to wildlife could potentially occur if there were greater than 3 ppt dioxin in their diet. DOC ER 47, AR No. 144, at 13-33. The concentration of dioxin in fish expected to occur through implementation of the TMDL is one forty-third of this value.[49/]

DOC expresses particular concern about possible impacts on bald eagles, DOC Br. at 8-9, 23-24, and alleges that "EPA never addressed any of these concerns," id. at 9, except by "abdicating" its responsibilities in favor of the USFWS. Id. at 24-25. By seeking the benefit of USFWS' expertise on wildlife issues, EPA

49/ The district court referred to this record document as support for EPA's finding that the TMDL would protect wildlife. CR 88 at 15, Mills ER 246. DOC strains to find error in the district court's reasoning by an irrelevant quotation from the document to the effect that insufficient data exist to derive a national aquatic life criterion for dioxin. DOC Br. at 22. DOC also distorts the facts by alleging that the 3 ppt fish residue value referenced in the Background Document was based on data showing that 3 ppt represented the "lowest observed adverse effects level," rather than a level at which no adverse effects are expected. DOC Br. at 22. To the contrary, that value was derived based on a dietary intake level in Rhesus monkeys found to have no adverse effect. See New York Department of Environmental Conservation ("NYDEC"), Niagara River Biota Contamination Project: Fish Flesh Criteria for Piscivorous Wildlife, at 71-72 (1987) (Appendix A hereto), cited in AR No. 144, at 13-33. Although not itself part of the administrative record, the NYDEC document may properly be considered for the limited purpose of explaining the meaning of the Background Document, which is in the record and which relied upon the NYDEC document.

was not "abdicating" its own responsibilities, but was instead seeking input from a sister agency with expertise in protection of endangered species.[50] EPA engaged in informal consultation with the USFWS before finalizing the TMDL to ensure that there would be no jeopardy to bald eagles as a result of implementation of the TMDL. AR No. 15, SER 2.[51] USFWS "commend[ed] the EPA in its actions to develop a total maximum daily load for dioxins in the Columbia River." AR No. 103 at 2, SER 15. Also, USFWS "agree[d] ... that the proposed reduction in dioxin discharges would not adversely affect any threatened or endangered species." AR No. 22, SER 4.[52] Thus, as the district court properly found, the administrative record provides sufficient evidence to support

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[50] EPA had also received public comments suggesting that consultation with USFWS was appropriate. AR No. 19(3) at 7-8, Mills ER 134-35; DOC ER Tab 47, AR No. 94.

[51] Whether EPA fully satisfied its obligations under the Endangered Species Act ("ESA") by engaging in informal consultation is not before this Court. As DOC notes, DOC Br. at 24 n.23, DOC settled its ESA claims against EPA in separate litigation. Thus, notwithstanding intimations in DOC's argument, e.g. DOC Br. at 23, no ESA issues are present in this case.

[52] DOC cites a formal biological opinion issued by USFWS in January 1994 for the proposition that the TMDL will not provide adequate protection for bald eagles. DOC Br. at 24 n.23. On March 1, 1994, the Court granted EPA's motion to strike that document from the record. That ruling was proper because the USFWS opinion was not part of the administrative record, and is based heavily on recent studies and data that were not available when EPA established the TMDL in early 1991. However, the Court allowed DOC's extra-record exhibit to remain "lodged" for such consideration as the merits panel deems necessary. While EPA does not believe that such post-decisional material may be properly considered for any purpose, we note that DOC has grossly mischaracterized USFWS' conclusions in that document. In fact, USFWS concluded that the establishment of the TMDL will not jeopardize the continued existence of the bald eagle, and recommended that EPA continue to implement the TMDL during the next five years while it gathers further data. DOC Appendix F at 2-3, 22.

EPA's conclusion that the TMDL will protect aquatic biota and wildlife. CR No. 88 at 15-16 & n.4, Mills ER 246-47 & n.4.

DOC claims that EPA never addressed USFWS' recommendation that EPA "strive toward . . . zero discharge." DOC Br. at 9, 23, 25. In fact, EPA did "strive" towards zero discharge by imposing a TMDL based on the limits of detection capability, and which requires a 95 percent reduction in pulp mill discharges of dioxin. EPA then explained why it rejected a zero discharge option: "All available information has been carefully considered. Based on that information the 'zero discharge' option is not necessary to achieve water quality standards . . . ." AR No. 19(2) at 3-9, Mills ER 102. DOC does not contest EPA's technical conclusion that it could not measure compliance with stricter wasteload allocations using currently available technology. Thus, EPA addressed the zero discharge option and provided adequate explanation of the basis for the choices it made.[53/]

V. EVEN IF THE COURT AGREES WITH DOC'S ARGUMENTS, THE TMDL SHOULD BE LEFT IN PLACE PENDING FURTHER AGENCY ACTION.

Even if the Court agrees with one or more of DOC's arguments and remands the TMDL to EPA to consider whether the TMDL should be redesigned to implement a more stringent water quality standard, the existing TMDL should be left in place pending revision. Vacatur of the TMDL would be counterproductive, because the TMDL provides substantially more protection to all users of the

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53/ Courts must uphold a decision even if it is of less than ideal clarity if the agency's path may reasonably be discerned. Northern Plains Resource Council v. EPA, 645 F.2d 1349, 1358 (9th Cir. 1981).

Columbia River, including the wildlife and human populations of concern to DOC, than the pre-TMDL regulatory regime.

As the D.C. Circuit recently recognized in the context of a notice and comment challenge, "when equity demands, an unlawfully promulgated regulation can be left in place while the agency provides the proper procedural remedy." Fertilizer Inst. v. EPA, 935 F.2d 1303, 1312 (D.C. Cir. 1991) (court allowed certain exemptions provided by EPA to remain in place pending full opportunity for notice and comment because vacating rules on remand may affect EPA's ability to respond adequately to serious safety hazards). As this Court has stated, judicial "intervention into the process of environmental regulation, a process of great complexity, should be accomplished with as little intrusiveness as feasible." Western Oil & Gas Ass'n v. EPA, 633 F.2d 803, 813 (9th Cir. 1980).54/ Similarly, in Chemical Mfrs. Ass'n v. EPA, 870 F.2d 177 (5th Cir. 1989), cert. denied, 495 U.S. 910 (1990), the Fifth Circuit left certain Clean Water Act effluent limitations in place pending full notice and comment, for three reasons equally applicable here:

54/ In Western Oil & Gas, the Court held that a reviewing court has discretion to shape an equitable remedy when reviewing agency regulations. There, the Court declined to invalidate certain Clean Air Act designations pending a fuller opportunity for notice and comment, based on the Court's "desire to avoid thwarting in an unnecessary way the operation of the Clean Air Act . . . during the time that the deliberative process is reenacted," and the "possibility of undesirable consequences which we cannot now predict that might result from invalidation of the designations." Id. at 813. See also Forelaws on Board v. Johnson, 743 F.2d 677, 685-86 (9th Cir. 1984) (refusing to enjoin ongoing agency contracts despite violation of National Environmental Policy Act), cert. denied, 478 U.S. 1004 (1986).

> First, we recognize Congress' concern for limiting the discharge of toxic pollutants within the statutory deadline. Second, the notice-and-comment proceedings may disclose that the . . . parameter urged by [petitioner environmental group] is neither necessary nor feasible. Finally, the industrial petitioners are not prejudiced by being subjected to . . . limitations which, if anything, may be too lenient.

Id. at 236. For the same reasons, the Court should leave the TMDL in effect on remand, even if it is persuaded by DOC's arguments that further consideration is appropriate.

CONCLUSION

The district court properly found that establishment of the Columbia River TMDL was not arbitrary or capricious, an abuse of discretion, or contrary to law. CR No. 88 at 18, Mills ER 249. For the foregoing reasons, that judgment should be affirmed.

Respectfully submitted,

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Dated: May 31, 1994

STATEMENT OF RELATED CASES

The only related case known to Defendant-Appellee is identified in the Brief of Appellants Longview Fibre Co., et al. at 4 and 21, and in the Brief of Appellants Dioxin/Organochlorine Center, et al., at 4 n.7.

CERTIFICATE OF SERVICE

I, Christopher S. Vaden, hereby certify that on May 31, 1994, I caused two true and correct copies of the foregoing Brief for the Defendants-Appellees to be served by Federal Express, overnight delivery, to:

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WASHINGTON STATE DEPARTMENT OF ECOLOGY

CR-102 Cover Sheet

Rule Citation(s) and Title(s):

Repealing Chapter 173-201WAC and replacing it with Chapter 173-201A WAC, Water Quality Standards for Surface Waters of the state of Washington.

Proposed Adoption Date:

October 7, 1992

Executive Summary (*attach separate sheet if necessary*):

Proposing revisions to the State's surface water quality standards regulation, Chapter 173-201 WAC.

Key elements of this revision include:

- Correction of typographic errors, restructuring of subsections, and minor language clarifications.
- Repealing and replacing the existing rule citation (173-201) as Chapter 173-201A WAC.
- Updating the State's antidegradation policy.
- Adopting aquatic life toxic criteria for four substances.
- Revised language clarifying the applicability of the standards to nonpoint sources and stormwater.
- Establishing criteria on allowing mixing zones for waste discharges.
- Upgrading Totten Inlet and Little Skookum Inlet and the Lower Cedar River to Class AA.
- Clarifying the intent to use toxicity testing and biological assessments to ensure aquatic life protection.
- Adding special temperature condition to the Skagit River George bypass.

Date signature required:

May 19, 1992

This filing package contains:

- ■ CR-102 Cover Sheet
- ■ Completed CR-102 Form
- ■ Small Business Economic Impact Statement
- ■ Proposed rules presented in OTS computer printout in WAC order

Reviewed by Rules Coordinator on:

(j) Short explanation of rule, its purpose, and anticipated effects:

The Department of Ecology is proposing revisions to the State's surface water quality standards regulation, Chapter 173-201 WAC. These revisions are designed to provide improved protection for water quality, in accordance with the purpose and authority established by Chapter 90.48 RCW, Water Pollution Control Act.

Does proposal change existing rules? ☒ YES ☐ NO If yes, describe changes:

Key elements of this revision include:
- Correction of typographic errors, restructuring of subsections, and minor language clarifications.
- Repealing and replacing the existing rule citation (173-201) as Chapter 173-201A WAC.
- Updating the State's antidegradation policy.
- Adopting aquatic life toxic Criteria for four substances.
- Revised language clarifying the applicability of the standards to nonpoint sources and stormwater.
- Establishing criteria on allowing mixing zones for waste discharges.
- ** See bottom of page for the rest.

(k) Is small business economic impact statement required by chapter 19.85 RCW? ☒ YES ☐ NO
(Use this space, if possible. Attach extra sheets if necessary.)

See attached SBEIS summaries.

- Upgrading Totten Inlet and Little Skookum Inlet and the Lower Cedar River to Class AA.
- Clarifying the intent to use toxicity testing and biological assessments to ensure aquatic life protection.
- Adding special temperature condition to the Skagit River Gorge Bypass.

CODE REVISER'S OFFICE
STATE OF WASHINGTON
FILED
MAY 19 1995
TIME
BY

SMALL BUSINESS ECONOMIC IMPACT STATEMENT

for

WATER QUALITY STANDARDS FOR SURFACE WATERS
OF THE STATE OF WASHINGTON
CHAPTER 173-201A WAC

SUMMARY

INTRODUCTION

This document summarizes the Small Business Economic Impact Statement (SBEIS) written for the amendments to the state surface water quality standards. The full SBEIS may be obtained from Ecology's Water Quality Program.

The state Regulatory Fairness Act requires that a SBEIS be written for rules which have an economic impact on more than twenty percent of all industries or more than ten percent of any one industry. The SBEIS must describe the costs of complying with the rule. It must compare the compliance costs of small and large businesses to determine whether the rule disproportionately impacts small business.

A small business is defined as a profit-seeking enterprise, which is independently owned and operated from all other businesses, and which has fifty or fewer employees.

AMENDMENTS TO THE SURFACE WATER QUALITY STANDARDS

The Clean Water Act requires that states review their surface water quality standards at least once every three years. As a result of this review, many amendments have been made to the standards. There are seven primary amendments to the standards that cause economic impacts:

1. Subsections 040(2): Whole Effluent Toxicity Testing and Bioassessments for Aquatic Life Protection.
2. Subsections 040(3): Additional Aquatic Life Criteria.
3. Subsection 040(6). Human Health Risk Level for Establishing Criteria for Carcinogens.
4. Section 100: Mixing Zones.
5. Subsection 130(6): Reclassification of Lower Cedar River.
6. Subsection 130(93): Special Condition for Skagit River.
7. Subsection 140(25): Reclassification of Totten Inlet.

AO# 92-29

PROPOSED RULE MAKING
(RCW 34.05.320)

CR-102 (7/1/89)

- [X] Original Notice
- [ ] Supplemental Notice to WSR _____
- [ ] Continuance of WSR _____

Agency: Department of Ecology

(a) Title of rule: (Describe Subject)

Repealing Chapter 173-201 WAC and replacing it with Chapter 173-201A WAC, Water Quality Standards for Surface Waters of the state of Washington.

Purpose:

To establish water quality standards for surface waters of the State consistent with public health and public enjoyment thereof, and the propogation and protection of fish, shellfish and wildlife, pursuant to the provisions of Chapter 90.48 RCW and the policies established thereof.

Other identifying information:

To improve the regulation's structural efficiency, it is necessary to change the title to new Chapter 173-201A.

(b) Statutory authority for adoption:	Statute being implemented:
Chapter 90.48 RCW	Chapter 90.48 RCW

(c) Summary: The Department of Ecology is proposing revisions to the State's surface water quality standards which will improve their effectiveness in protecting water quality in accordance with the purpose and authority established by Chapter 90.48 RCW, Water Pollution Control Act.

Reasons supporting proposal:

- Authority and mandate to protect Water Quality as established by Chapter 90.48 RCW.
- State Committments to the USEPA to carry out provisions of the Clean Water Act.
- Revisions consistent with existing state standards for the protection of Surface Water.

(d) Name of Agency Personnel Responsible For:

		Office Location	Telephone
1. Drafting	Mark Hicks	Prudential Building	438-7087
2. Implementation	Michael T. Llewelyn	Prudential Building	438-7090
3. Enforcement	Michael T. Llewelyn	Prudential Building	438-7090

(e) Name of proponent (person or organization)

Department of Ecology

- [ ] Private
- [ ] Public
- [X] Governmental

(f) Agency comments or recommendations, if any, as to statutory language, implementation, enforcement, and fiscal matters:

This rule has complied with the requirements of RCW 90.70.080.

(g) Is rule necessary because of:

Federal Law?	[X] Yes [ ] No	If yes, *ATTACH COPY OF TEXT*	Federal Water Pollution Control Act, as amedned by the Clean Water Act of 1977. (See attached reproduction of the relevant Section 303(c).)
Federal Court Decision?	[ ] Yes [ ] No	Citation:	
State Court Decision?	[ ] Yes [ ] No		

(h) HEARING LOCATION:

July 21: Moses Lake, Washington, PUD Auditorium, 312 W 3rd, 7:00 pm

July 22: Bellevue, Washington, Ecology NWRO, 3190 160th Ave SE, 7:00 pm

Date: July 21 & 22, 1992 Time: 7:00 pm

Submit written comments to:

Mark Hicks
Water Quality Program
Dept. of Ecology PO Box 47600 By (date): 7/30/92

DATE OF INTENDED ADOPTION:

October 7, 1992

CODE REVISER USE ONLY

CODE REVISER'S OFFICE
STATE OF WASHINGTON
FILED

MAY 19 1992

TIME 9:03 AM

WSR 92-11-041

00971

1E (TYPE OR PRINT)

Fred Olson

SIGNATURE

Fred Ols

TITLE

Deputy Director

DATE

5/18/92

(COMPLETE REVERSE SIDE)

WSR 97-23-064

PERMANENT RULES

DEPARTMENT OF ECOLOGY

[Order 94-19--Filed November 18, 1997, 4:04 p.m.]

Date of Adoption: November 18, 1997.

Purpose: To amend chapter 173-201A WAC to update the standards, streamline language, add new language to improve and solve water quality problems, and to clarify rule language changes.

Citation of Existing Rules Affected by this Order: Amending chapter 173-201A WAC, the surface water quality standards.

Statutory Authority for Adoption: Chapter 90.48 RCW.

Other Authority: 40 CFR 131.

Adopted under notice filed as WSR 97-12-034 on May 30, 1997.

Changes Other than Editing from Proposed to Adopted Version: Additional language has been added to the definitions for "action value," "lake specific-study," and "trophic state." Some language was amended and changed in WAC 173-201A-030(6) for lake nutrient criteria guidance. WAC 173-201A-040 for toxic substances had some minor numeric changes and changes to footnotes affecting where the criteria applied. There was a minor language change to WAC 173-201A-060 (2) and (4)(c) and language added to WAC 173-201A-110 (1)(c).

Number of Sections Adopted in Order to Comply with Federal Statute: New 0, amended 0, repealed 0; Federal Rules or Standards: New 0, amended 8, repealed 0; or Recently Enacted State Statutes: New 0, amended 0, repealed 0.

Number of Sections Adopted at Request of a Nongovernmental Entity: New 0, amended 2, repealed 0.

Number of Sections Adopted on the Agency's own Initiative: New 0, amended 8, repealed 0.

Number of Sections Adopted in Order to Clarify, Streamline, or Reform Agency Procedures: New 0, amended 8, repealed 0.

Number of Sections Adopted using Negotiated Rule Making: New 0, amended 0, repealed 0; Pilot Rule Making: New 0, amended 0, repealed 0; or Other Alternative Rule Making: New 0, amended 0, repealed 0.

Effective Date of Rule: Thirty-one days after filing.

November 18, 1997

Tom Fitzsimmons

Director

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-020 Definitions. The following definitions are intended to facilitate the use of chapter 173-201A WAC:

"Action value" means a total phosphorus (TP) value established at the upper limit of the trophic states in each ecoregion. Exceedance of an action value indicates that a problem is suspected. A lake-specific study may be needed to confirm if a nutrient problem exits.

"Acute conditions" are changes in the physical, chemical, or biologic environment which are expected or demonstrated to result in injury or death to an organism as a result of short-term exposure to the substance or detrimental environmental condition.

"AKART" is an acronym for "all known, available, and reasonable methods of prevention, control, and treatment." AKART shall represent the most current methodology that can be reasonably required for preventing, controlling, or abating the pollutants associated with a discharge. The concept of AKART applies to both point and nonpoint sources of pollution. The term "best management practices," typically applied to nonpoint source pollution controls is considered a subset of the AKART requirement. "The Stormwater Management Manual for the Puget Sound Basin" (1992), may be used as a guideline, to the extent appropriate, for developing best management practices to apply AKART for storm water discharges.

"Background conditions" means the biological, chemical, and physical conditions of a water body, outside the area of influence of the discharge under consideration. Background sampling locations in an enforcement action would be up-gradient or outside the area of influence of the discharge. If several discharges to any water body exist, and enforcement action is being taken for possible violations to the standards, background sampling would be undertaken immediately up-gradient from each discharge. When assessing background conditions in the headwaters of a disturbed watershed it may be necessary to use the background conditions of a neighboring or similar watershed as the reference conditions.

"Best management practices (BMP)" means physical, structural, and/or managerial practices approved by the department that, when used singularly or in combination, prevent or reduce pollutant discharges.

"Biological assessment" is an evaluation of the biological condition of a water body using surveys of aquatic community structure and function and other direct measurements of resident biota in surface waters.

"Bog" means those wetlands that are acidic, peat forming, and whose primary water source is precipitation, with little, if any, outflow.

"Carcinogen" means any substance or agent that produces or tends to produce cancer in humans. For implementation of this chapter, the term carcinogen will apply to substances on the United States Environmental Protection Agency lists of A (known human) and B (probable human) carcinogens, and any substance which causes a significant increased incidence of benign or malignant tumors in a single, well conducted animal bioassay, consistent with the weight of evidence approach specified in the United States Environmental Protection Agency's Guidelines for Carcinogenic Risk Assessment as set forth in 51 FR 33992 et seq. as presently published or as subsequently amended or republished.

"Chronic conditions" are changes in the physical, chemical, or biologic environment which are expected or demonstrated to result in injury or death to an organism as a result of repeated or constant exposure over an extended period of time to a substance or detrimental environmental condition.

"Created wetlands" means those wetlands intentionally created from nonwetland sites to produce or replace natural wetland habitat.

"Critical condition" is when the physical, chemical, and biological characteristics of the receiving water environment interact with the effluent to produce the greatest

potential adverse impact on aquatic biota and existing or characteristic water uses. For steady-state discharges to riverine systems the critical condition may be assumed to be equal to the ((~~7010~~)) 7Q10 flow event unless determined otherwise by the department.

"Damage to the ecosystem" means any demonstrated or predicted stress to aquatic or terrestrial organisms or communities of organisms which the department reasonably concludes may interfere in the health or survival success or natural structure of such populations. This stress may be due to, but is not limited to, alteration in habitat or changes in water temperature, chemistry, or turbidity, and shall consider the potential build up of discharge constituents or temporal increases in habitat alteration which may create such stress in the long term.

"Department" means the state of Washington department of ecology.

"Director" means the director of the state of Washington department of ecology.

"Drainage ditch" means that portion of a designed and constructed conveyance system that serves the purpose of transporting surplus water; this may include natural water courses or channels incorporated in the system design, but does not include the area adjacent to the water course or channel.

"Ecoregions" are defined using EPAs *Ecoregions of the Pacific Northwest* Document No. 600/3-86/033 July 1986 by Omernik and Gallant.

"Fecal coliform" means that portion of the coliform group which is present in the intestinal tracts and feces of warm-blooded animals as detected by the product of acid or gas from lactose in a suitable culture medium within twenty-four hours at 44.5 plus or minus 0.2 degrees Celsius.

"Geometric mean" means either the nth root of a product of n factors, or the antilogarithm of the arithmetic mean of the logarithms of the individual sample values.

"Ground water exchange" means the discharge and recharge of ground water to a surface water. Discharge is inflow from an aquifer, seeps or springs that increases the available supply of surface water. Recharge is outflow downgradient to an aquifer or downstream to surface water for base flow maintenance. Exchange may include ground water discharge in one season followed by recharge later in the year.

"Hardness" means a measure of the calcium and magnesium salts present in water. For purposes of this chapter, hardness is measured in milligrams per liter and expressed as calcium carbonate ($CaCO_3$).

"Irrigation ditch" means that portion of a designed and constructed conveyance system that serves the purpose of transporting irrigation water from its supply source to its place of use; this may include natural water courses or channels incorporated in the system design, but does not include the area adjacent to the water course or channel.

"Lakes" shall be distinguished from riverine systems as being water bodies, including reservoirs, with a mean detention time of greater than fifteen days.

"Lake-specific study" means a study intended to quantify existing nutrient concentrations, determine existing characteristic uses for lake class waters, and potential lake uses. The study determines how to protect these uses and if any uses are lost or impaired because of nutrients, algae, or aquatic plants. An appropriate study must recommend a criterion for total phosphorus (TP), total nitrogen (TN) in g/l, or other nutrient that impairs characteristic uses by causing excessive algae blooms or aquatic plant growth.

"Mean detention time" means the time obtained by dividing a reservoir's mean annual minimum total storage by the thirty-day ten-year low-flow from the reservoir.

"Migration or translocation" means any natural movement of an organism or community of organisms from one locality to another locality.

"Mixing zone" means that portion of a water body adjacent to an effluent outfall where mixing results in the dilution of the effluent with the receiving water. Water quality criteria may be exceeded in a mixing zone as conditioned and provided for in WAC 173-201A-100.

"Natural conditions" or "natural background levels" means surface water quality that was present before any human-caused pollution. When estimating natural conditions in the headwaters of a disturbed watershed it may be necessary to use the less disturbed conditions of a neighboring or similar watershed as a reference condition.

"Nonpoint source" means pollution that enters any waters of the state from any dispersed land-based or water-based activities, including but not limited to atmospheric deposition, surface water runoff from agricultural lands, urban areas,

or forest lands, subsurface or underground sources, or discharges from boats or marine vessels not otherwise regulated under the National Pollutant Discharge Elimination System program.

"Permit" means a document issued pursuant to RCW 90.48.160 et seq. or RCW 90.48.260 or both, specifying the waste treatment and control requirements and waste discharge conditions.

"pH" means the negative logarithm of the hydrogen ion concentration.

"Pollution" means such contamination, or other alteration of the physical, chemical, or biological properties, of any waters of the state, including change in temperature, taste, color, turbidity, or odor of the waters, or such discharge of any liquid, gaseous, solid, radioactive, or other substance into any waters of the state as will or is likely to create a nuisance or render such waters harmful, detrimental, or injurious to the public health, safety, or welfare, or to domestic, commercial, industrial, agricultural, recreational, or other legitimate beneficial uses, or to livestock, wild animals, birds, fish, or other aquatic life.

"Primary contact recreation" means activities where a person would have direct contact with water to the point of complete submergence including, but not limited to, skin diving, swimming, and water skiing.

"Secondary contact recreation" means activities where a person's water contact would be limited (wading or fishing) to the extent that bacterial infections of eyes, ears, respiratory or digestive systems, or urogenital areas would normally be avoided.

"Shoreline stabilization" means the anchoring of soil at the water's edge, or in shallow water, by fibrous plant root complexes; this may include long-term accretion of sediment or peat, along with shoreline progradation in such areas.

"Storm water" means that portion of precipitation that does not naturally percolate into the ground or evaporate, but flows via overland flow, interflow, pipes, and other features of a storm water drainage system into a defined surface water body, or a constructed infiltration facility.

"Storm water attenuation" means the process by which peak flows from precipitation are reduced and runoff velocities are slowed as a result of passing through a surface waterbody.

"Surface waters of the state" includes lakes, rivers, ponds, streams, inland waters,

saltwaters, wetlands and all other surface waters and water courses within the jurisdiction of the state of Washington.

"Temperature" means water temperature expressed in degrees Celsius (C).

"Treatment wetlands" means those wetlands intentionally constructed on nonwetland sites and managed for the primary purpose of wastewater or storm water treatment. Treatment wetlands are considered part of a collection and treatment system, and generally are not subject to the criteria of this chapter.

"Trophic state" means a classification of the productivity of a lake ecosystem. Lake productivity depends on the amount of biologically available nutrients in water and sediments and may be based on total phosphorus (TP). Secchi depth and chlorophyll-a measurements may be used to improve the trophic state classification of a lake. Trophic states used in this rule include, from least to most nutrient rich, ultra-oligotrophic, oligotrophic, lower mesotrophic, upper mesotrophic, and eutrophic.

"Turbidity" means the clarity of water expressed as nephelometric turbidity units (NTU) and measured with a calibrated turbidimeter.

"Upwelling" means the natural process along Washington's Pacific Coast where the summer prevailing northerly winds produce a seaward transport of surface water. Cold, deeper more saline waters rich in nutrients and low in dissolved oxygen, rise to replace the surface water. The cold oxygen deficient water enters Puget Sound and other coastal ((~~estauries~~)) estuaries at depth where it displaces the existing deep water and eventually rises to replace the surface water. Such surface water replacement results in an overall increase in salinity and nutrients accompanied by a depression in dissolved oxygen. Localized upwelling of the deeper water of Puget Sound can occur year-round under influence of tidal currents, winds, and geomorphic features.

"USEPA" means the United States Environmental Protection Agency.

"Wetlands" means areas that are inundated or saturated by surface water or ground water at a frequency and duration sufficient to support, and that under normal circumstances do support, a prevalence of vegetation typically adapted for life in saturated soil conditions. Wetlands generally include swamps, marshes, bogs, and similar areas. Wetlands do not include those artificial wetlands intentionally created from nonwetland sites, including, but not limited to, irrigation and drainage ditches, grass-lined swales, canals, detention facilities, wastewater treatment facilities, farm ponds, and landscape amenities, or those wetlands

created after July 1, 1990, that were unintentionally created as a result of the construction of a road, street, or highway. Wetlands may include those artificial wetlands intentionally created from nonwetland areas to mitigate the conversion of wetlands. (Waterbodies not included in the definition of wetlands as well as those mentioned in the definition are still waters of the state.)

"Wildlife habitat" means waters of the state used by, or that directly or indirectly provide food support to, fish, other aquatic life, and wildlife for any life history stage or activity.

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-020, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-030 General water use and criteria classes. The following criteria shall apply to the various classes of surface waters in the state of Washington:

(1) **Class AA (extraordinary).**

(a) General characteristic. Water quality of this class shall markedly and uniformly exceed the requirements for all or substantially all uses.

(b) Characteristic uses. Characteristic uses shall include, but not be limited to, the following:

(i) Water supply (domestic, industrial, agricultural).

(ii) Stock watering.

(iii) Fish and shellfish:

Salmonid migration, rearing, spawning, and harvesting.

Other fish migration, rearing, spawning, and harvesting.

Clam, oyster, and mussel rearing, spawning, and harvesting.

Crustaceans and other shellfish (crabs, shrimp, crayfish, scallops, etc.) rearing,

spawning, and harvesting.

(iv) Wildlife habitat.

(v) Recreation (primary contact recreation, sport fishing, boating, and aesthetic enjoyment).

(vi) Commerce and navigation.

(c) Water quality criteria:

(i) Fecal coliform organisms:

(A) Freshwater - fecal coliform organism levels shall both not exceed a geometric mean value of 50 colonies/100 mL and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 100 colonies/100 mL.

(B) Marine water - fecal coliform organism levels shall both not exceed a geometric mean value of 14 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 43 colonies/100 mL.

(ii) Dissolved oxygen:

(A) Freshwater - dissolved oxygen shall exceed 9.5 mg/L.

(B) Marine water - dissolved oxygen shall exceed 7.0 mg/L. When natural conditions, such as upwelling, occur, causing the dissolved oxygen to be depressed near or below 7.0 mg/L, natural dissolved oxygen levels may be degraded by up to 0.2 mg/L by human-caused activities.

(iii) Total dissolved gas shall not exceed 110 percent of saturation at any point of sample collection.

(iv) Temperature shall not exceed 16.0C (freshwater) or 13.0C (marine water) due to human activities. When natural conditions exceed 16.0C (freshwater) and 13.0C (marine water), no temperature increases will be allowed which will raise the receiving water temperature by greater than 0.3C.

Incremental temperature increases resulting from point source activities shall not,

at any time, exceed t=23/(T+5) (freshwater) or t=8/(T-4) (marine water). Incremental temperature increases resulting from nonpoint source activities shall not exceed 2.8C.

For purposes hereof, "t" represents the maximum permissible temperature increase measured at a mixing zone boundary; and "T" represents the background temperature as measured at a point or points unaffected by the discharge and representative of the highest ambient water temperature in the vicinity of the discharge.

(v) pH shall be within the range of 6.5 to 8.5 (freshwater) or 7.0 to 8.5 (marine water) with a human-caused variation within ((~~a~~)) the above range of less than 0.2 units.

(vi) Turbidity shall not exceed 5 NTU over background turbidity when the background turbidity is 50 NTU or less, or have more than a 10 percent increase in turbidity when the background turbidity is more than 50 NTU.

(vii) Toxic, radioactive, or deleterious material concentrations shall be below those which have the potential either singularly or cumulatively to adversely affect characteristic water uses, cause acute or chronic conditions to the most sensitive biota dependent upon those waters, or adversely affect public health, as determined by the department (see WAC 173-201A-040 and 173-201A-050).

(viii) Aesthetic values shall not be impaired by the presence of materials or their effects, excluding those of natural origin, which offend the senses of sight, smell, touch, or taste.

(2) **Class A (excellent).**

(a) General characteristic. Water quality of this class shall meet or exceed the requirements for all or substantially all uses.

(b) Characteristic uses. Characteristic uses shall include, but not be limited to, the following:

(i) Water supply (domestic, industrial, agricultural).

(ii) Stock watering.

(iii) Fish and shellfish:

Salmonid migration, rearing, spawning, and harvesting.

Other fish migration, rearing, spawning, and harvesting.

Clam, oyster, and mussel rearing, spawning, and harvesting.

Crustaceans and other shellfish (crabs, shrimp, crayfish, scallops, etc.) rearing, spawning, and harvesting.

(iv) Wildlife habitat.

(v) Recreation (primary contact recreation, sport fishing, boating, and aesthetic enjoyment).

(vi) Commerce and navigation.

(c) Water quality criteria:

(i) Fecal coliform organisms:

(A) Freshwater - fecal coliform organism levels shall both not exceed a geometric mean value of 100 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 200 colonies/100 mL.

(B) Marine water - fecal coliform organism levels shall both not exceed a geometric mean value of 14 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 43 colonies/100 mL.

(ii) Dissolved oxygen:

(A) Freshwater - dissolved oxygen shall exceed 8.0 mg/L.

(B) Marine water - dissolved oxygen shall exceed 6.0 mg/L. When natural conditions, such as upwelling, occur, causing the dissolved oxygen to be depressed near or below 6.0 mg/L, natural dissolved oxygen levels may be degraded by up to 0.2 mg/L by human-caused activities.

(iii) Total dissolved gas shall not exceed 110 percent of saturation at any point of sample collection.

(iv) Temperature shall not exceed 18.0C (freshwater) or 16.0C (marine water) due to human activities. When natural conditions exceed 18.0C (freshwater) and 16.0C (marine water), no temperature increases will be allowed which will raise the receiving water temperature by greater than 0.3C.

Incremental temperature increases resulting from point source activities shall not, at any time, exceed t=28/(T+7) (freshwater) or t=12/(T-2) (marine water). Incremental temperature increases resulting from nonpoint source activities shall not exceed 2.8C.

For purposes hereof, "t" represents the maximum permissible temperature increase measured at a mixing zone boundary; and "T" represents the background temperature as measured at a point or points unaffected by the discharge and representative of the highest ambient water temperature in the vicinity of the discharge.

(v) pH shall be within the range of 6.5 to 8.5 (freshwater) or 7.0 to 8.5 (marine water) with a human-caused variation within ((~~a~~)) the above range of less than 0.5 units.

(vi) Turbidity shall not exceed 5 NTU over background turbidity when the background turbidity is 50 NTU or less, or have more than a 10 percent increase in turbidity when the background turbidity is more than 50 NTU.

(vii) Toxic, radioactive, or deleterious material concentrations shall be below those which have the potential either singularly or cumulatively to adversely affect characteristic water uses, cause acute or chronic conditions to the most sensitive biota dependent upon those waters, or adversely affect public health, as determined by the department (see WAC 173-201A-040 and 173-201A-050).

(viii) Aesthetic values shall not be impaired by the presence of materials or their effects, excluding those of natural origin, which offend the senses of sight, smell, touch, or taste.

(3) **Class B (good).**

(a) General characteristic. Water quality of this class shall meet or exceed the requirements for most uses.

(b) Characteristic uses. Characteristic uses shall include, but not be limited to, the following:

(i) Water supply (industrial and agricultural).

(ii) Stock watering.

(iii) Fish and shellfish:

Salmonid migration, rearing, and harvesting.

Other fish migration, rearing, spawning, and harvesting.

Clam, oyster, and mussel rearing and spawning.

Crustaceans and other shellfish (crabs, shrimp, crayfish, scallops, etc.) rearing, spawning, and harvesting.

(iv) Wildlife habitat.

(v) Recreation (secondary contact recreation, sport fishing, boating, and aesthetic enjoyment).

(vi) Commerce and navigation.

(c) Water quality criteria:

(i) Fecal coliform organisms:

(A) Freshwater - fecal coliform organism levels shall both not exceed a geometric mean value of 200 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 400 colonies/100 mL.

(B) Marine water - fecal coliform organism levels shall both not exceed a geometric mean value of 100 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 200 colonies/100 Ml.

(ii) Dissolved oxygen:

(A) Freshwater - dissolved oxygen shall exceed 6.5 mg/L.

(B) Marine water - dissolved oxygen shall exceed 5.0 mg/L. When natural

conditions, such as upwelling, occur, causing the dissolved oxygen to be depressed near or below 5.0 mg/L, natural dissolved oxygen levels may be degraded by up to 0.2 mg/L by human-caused activities.

(iii) Total dissolved gas shall not exceed 110 percent of saturation at any point of sample collection.

(iv) Temperature shall not exceed 21.0C (freshwater) or 19.0C (marine water) due to human activities. When natural conditions exceed 21.0C (freshwater) and 19.0C (marine water), no temperature increases will be allowed which will raise the receiving water temperature by greater than 0.3C.

Incremental temperature increases resulting from point source activities shall not, at any time, exceed t=34/(T+9) (freshwater) or t=16/(T) (marine water). Incremental temperature increases resulting from nonpoint source activities shall not exceed 2.8C.

For purposes hereof, "t" represents the maximum permissible temperature increase measured at a mixing zone boundary; and "T" represents the background temperature as measured at a point or points unaffected by the discharge and representative of the highest ambient water temperature in the vicinity of the discharge.

(v) pH shall be within the range of 6.5 to 8.5 (freshwater) and 7.0 to 8.5 (marine water) with a human-caused variation within ((~~a~~)) the above range of less than 0.5 units.

(vi) Turbidity shall not exceed 10 NTU over background turbidity when the background turbidity is 50 NTU or less, or have more than a 20 percent increase in turbidity when the background turbidity is more than 50 NTU.

(vii) Toxic, radioactive, or deleterious material concentrations shall be below those which have the potential either singularly or cumulatively to adversely affect characteristic water uses, cause acute or chronic conditions to the most sensitive biota dependent upon those waters, or adversely affect public health, as determined by the department (see WAC 173-201A-040 and 173-201A-050).

(viii) Aesthetic values shall not be reduced by dissolved, suspended, floating, or submerged matter not attributed to natural causes, so as to affect water use or taint the flesh of edible species.

(4) **Class C (fair).**

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(a) General characteristic. Water quality of this class shall meet or exceed the requirements of selected and essential uses.

(b) Characteristic uses. Characteristic uses shall include, but not be limited to, the following:

(i) Water supply (industrial).

(ii) Fish (salmonid and other fish migration).

(iii) Recreation (secondary contact recreation, sport fishing, boating, and aesthetic enjoyment).

(iv) Commerce and navigation.

(c) Water quality criteria - marine water:

(i) Fecal coliform organism levels shall both not exceed a geometric mean value of 200 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 400 colonies/100 mL.

(ii) Dissolved oxygen shall exceed 4.0 mg/L. When natural conditions, such as upwelling, occur, causing the dissolved oxygen to be depressed near or below 4.0 mg/L, natural dissolved oxygen levels may be degraded by up to 0.2 mg/L by human-caused activities.

(iii) Temperature shall not exceed 22.0C due to human activities. When natural conditions exceed 22.0C, no temperature increases will be allowed which will raise the receiving water temperature by greater than 0.3C.

Incremental temperature increases shall not, at any time, exceed $t=20/(T+2)$.

For purposes hereof, "t" represents the maximum permissible temperature increase measured at a mixing zone boundary; and "T" represents the background temperature as measured at a point or points unaffected by the discharge and representative of the highest ambient water temperature in the vicinity of the discharge.

(iv) pH shall be within the range of 6.5 to 9.0 with a human-caused variation within a range of less than 0.5 units.

(v) Turbidity shall not exceed 10 NTU over background turbidity when the background turbidity is 50 NTU or less, or have more than a 20 percent increase in turbidity when the background turbidity is more than 50 NTU.

(vi) Toxic, radioactive, or deleterious material concentrations shall be below those which have the potential either singularly or cumulatively to adversely affect characteristic water uses, cause acute or chronic conditions to the most sensitive biota dependent upon those waters, or adversely affect public health, as determined by the department (see WAC 173-201A-040 and 173-201A-050).

(vii) Aesthetic values shall not be interfered with by the presence of obnoxious wastes, slimes, aquatic growths, or materials which will taint the flesh of edible species.

(5) **Lake class.**

(a) General characteristic. Water quality of this class shall meet or exceed the requirements for all or substantially all uses.

(b) Characteristic uses. Characteristic uses shall include, but not be limited to, the following:

(i) Water supply (domestic, industrial, agricultural).

(ii) Stock watering.

(iii) Fish and shellfish:

Salmonid migration, rearing, spawning, and harvesting.

Other fish migration, rearing, spawning, and harvesting.

Clam and mussel rearing, spawning, and harvesting.

Crayfish rearing, spawning, and harvesting.

(iv) Wildlife habitat.

(v) Recreation (primary contact recreation, sport fishing, boating, and aesthetic enjoyment).

(vi) Commerce and navigation.

(c) Water quality criteria:

(i) Fecal coliform organism levels shall both not exceed a geometric mean value of 50 colonies/100 mL, and not have more than 10 percent of all samples obtained for calculating the geometric mean value exceeding 100 colonies/100 mL.

(ii) Dissolved oxygen - no measurable decrease from natural conditions.

(iii) Total dissolved gas shall not exceed 110 percent of saturation at any point of sample collection.

(iv) Temperature - no measurable change from natural conditions.

(v) pH - no measurable change from natural conditions.

(vi) Turbidity shall not exceed 5 NTU over background conditions.

(vii) Toxic, radioactive, or deleterious material concentrations shall be below those which have the potential either singularly or cumulatively to adversely affect characteristic water uses, cause acute or chronic conditions to the most sensitive biota dependent upon those waters, or adversely affect public health, as determined by the department (see WAC 173-201A-040 and 173-201A-050).

(viii) Aesthetic values shall not be impaired by the presence of materials or their effects, excluding those of natural origin, which offend the senses of sight, smell, touch, or taste.

(6) **Establishing lake nutrient criteria.**

(a) The following table shall be used to aid in establishing nutrient criteria:

[Open Style:Columns Off]

(WAC 173-201A-030, Table 1)

[Open Style:Columns On]

Lakes in the Willamette, East Cascade Foothills, or Blue Mountain ecoregions do not have recommended values and need to have lake-specific studies in order to receive criteria as described in (c)(i) of this subsection.

(b) The following actions are recommended if ambient monitoring of a lake shows the epilimnetic total phosphorus concentration, as shown in Table 1 of this section, is below the action value for an ecoregion:

(i) Determine trophic status from existing or newly gathered data. The recommended minimum sampling to determine trophic status is calculated as the mean of four or more samples collected from the epilimnion between June through September in one or more consecutive years. Sampling must be spread throughout the season.

(ii) Propose criteria at or below the upper limit of the trophic state; or

(iii) Conduct lake-specific study to determine and propose to adopt appropriate criteria as described in (c) of this subsection.

(c) The following actions are recommended if ambient monitoring of a lake shows total phosphorus to exceed the action value for an ecoregion shown in Table 1 of this section or where recommended ecoregional action values do not exist:

(i) Conduct a lake-specific study to evaluate the characteristic uses of the lake. A lake-specific study may vary depending on the source or threat of impairment. Phytoplankton blooms, toxic phytoplankton, or excessive aquatic plants, are examples of various sources of impairment. The following are examples of quantitative measures that a study may describe: Total phosphorus, total nitrogen, chlorophyll-a, dissolved oxygen in the hypolimnion if thermally stratified, pH, hardness, or other measures of existing conditions and potential changes in any one of these parameters.

(ii) Determine appropriate total phosphorus concentrations or other nutrient criteria to protect characteristic lake uses. If the existing total phosphorus concentration is protective of characteristic lake uses, then set criteria at existing total phosphorus concentration. If the existing total phosphorus concentration is not protective of the existing characteristic lake uses, then set criteria at a protective concentration. Proposals to adopt appropriate total phosphorus criteria to protect characteristic uses must be developed by considering technical information and stakeholder input as part of a public involvement process equivalent to the Administrative Procedure Act (chapter 34.05 RCW).

(iii) Determine if the proposed total phosphorus criteria necessary to protect characteristic uses is achievable. If the recommended criterion is not achievable and if the characteristic use the criterion is intended to protect is not an existing use, then a higher criterion may be proposed in conformance with 40 CFR part 131.10.

(d) The department will consider proposed lake-specific nutrient criteria during any water quality standards rule making that follows development of a proposal. Adoption by rule formally establishes the criteria for that lake.

(e) Prioritization and investigation of lakes by the department will be initiated by listing problem lakes in a watershed needs assessment, and scheduled as part of the water quality program's watershed approach to pollution control. This prioritization will apply to lakes identified as warranting a criteria based on the results of a lake-specific study, to lakes warranting a lake-specific study for establishing criteria, and to lakes requiring restoration and pollution control measures due to exceedance of an established criterion. The adoption of nutrient criteria are generally not intended to apply to lakes or ponds with a surface area smaller than five acres; or to ponds wholly contained on private property owned and surrounded by a single landowner; and nutrients do not drain or leach from these lakes or private ponds to the detriment of other property owners or other water bodies; and do not impact designated uses in the lake. However, if the landowner proposes criteria the department may consider adoption.

(f) The department may not need to set a lake-specific criteria or further investigate a lake if existing water quality conditions are naturally poorer (higher TP) than the action value and uses have not been lost or degraded, per WAC 173-201A-070(2).

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-030, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-040 Toxic substances. (1) Toxic substances shall not be introduced above natural background levels in waters of the state which have the potential either singularly or cumulatively to adversely affect characteristic water uses, cause acute or chronic toxicity to the most sensitive biota dependent upon those waters, or adversely affect public health, as determined by the department.

(2) The department shall employ or require chemical testing, acute and chronic

toxicity testing, and biological assessments, as appropriate, to evaluate compliance with subsection (1) of this section and to ensure that aquatic communities and the existing and characteristic beneficial uses of waters are being fully protected.

(3) The following criteria shall be applied to all surface waters of the state of Washington for the protection of aquatic life. The department may revise the following criteria on a state-wide or waterbody-specific basis as needed to protect aquatic life occurring in waters of the state and to increase the technical accuracy of the criteria being applied. The department shall formally adopt any appropriate revised criteria as part of this chapter in accordance with the provisions established in chapter 34.05 RCW, the Administrative Procedure Act. The department shall ensure there are early opportunities for public review and comment on proposals to develop revised criteria. Values are g/L for all substances except Ammonia and Chloride which are mg/L:

Freshwater Marine Water

Substance Acute Chronic Acute Chronic

Aldrin/Dieldrin 2.5a 0.0019b 0.71a 0.0019b

Ammonia f,c g,d 0.233h,c 0.035h,d

(un-ionized NH3) hh

Arsenic ((~~ff~~)) dd 360.0c 190.0d ((~~69.0c 36.0d,cc~~))

69.0c,ll 36.0d,cc,ll

Cadmium dd i,c j,d ((~~37.2c 8.0d~~))

42.0c 9.3d

Chlordane 2.4a 0.0043b 0.09a 0.004b

Chloride (Dissolved) k 860.0h,c 230.0h,d - -

Chlorine (Total Residual) 19.0c 11.0d 13.0c 7.5d

((~~Chloropyrifos~~)) 0.083c 0.041d 0.011c 0.0056d

Chlorpyrifos

Chromium (Hex) dd ((~~16.0c1 11.0d 1,100.0c,1 50.0d~~))

15.0c,l,ii 10.0d,jj 1,100.0c,l,ll 50.0d,ll

Chromium (Tri) gg m,c n,d - -

Copper dd o,c p,d ((~~2.5c -~~))

4.8c,ll 3.1d,ll

Cyanide ee 22.0c 5.2d ((~~1.0c -~~))

1.0c,mm -

DDT (and metabolites) 1.1a 0.001b 0.13a 0.001b

Dieldrin/Aldrin e 2.5a 0.0019b 0.71a 0.0019b

Endosulfan 0.22a 0.056b 0.034a 0.0087b

Endrin 0.18a 0.0023b 0.037a 0.0023b

Heptachlor 0.52a 0.0038b 0.053a 0.0036b

Hexachlorocyclohexane

(Lindane) 2.0a 0.08b 0.16a -

Lead dd q,c r,d ((~~151.1c 5.8d~~))

210.0c,ll 8.1d,ll

Mercury s((~~, ff 2.4c 0.012d 2.1c 0.025d~~))

2.1c,kk,dd 0.012d,ff 1.8c,ll,dd 0.025d,ff

Nickel dd t,c u,d ((~~71.3c 7.9d~~))

74.0c,ll 8.2d,ll

Parathion 0.065c 0.013d - -

Pentachlorophenol (PCP) w,c v,d 13.0c 7.9d

Polychlorinated

Biphenyls (PCBs) 2.0b 0.014b 10.0b 0.030b

Selenium ((ff)) 20.0c,ff 5.0d,ff ((~~300.0c 71.0d,x~~))

290c,ll,dd 71.0d,x,ll,dd

Silver dd y,a - ((~~1.2a~~)) -

1.9a,ll

Toxaphene 0.73c,z 0.0002d 0.21c,z 0.0002d

Zinc dd aa,c bb,d ((~~84.6c 76.6d~~))

90.0c,ll 81.0d,ll

Notes to Table:

a. An instantaneous concentration not to be exceeded at any time.

b. A 24-hour average not to be exceeded.

c. A 1-hour average concentration not to be exceeded more than once every three years on the average.

d. A 4-day average concentration not to be exceeded more than once every three years on the average.

e. Aldrin is metabolically converted to Dieldrin. Therefore, the sum of the Aldrin and Dieldrin concentrations are compared with the Dieldrin criteria.

f. Shall not exceed the numerical value given by:

((~~0.52~~

~~----------~~

~~(FT)(FPH)(2)~~))

0.52 (FT)(FPH)(2)

where: FT = $10^{[0.03(20-TCAP)]}$; TCAP T 30

FT = $10^{[0.03(20-T)]}$; 0 T TCAP

FPH = 1 ; 8 pH 9

FPH = ((~~1+10$^{(7.4-pH)}$~~)) (1 + 10$^{(7.4-pH)}$) 1.25 ; 6.5 pH 8.0

((~~----------~~

~~1.25~~))

TCAP = 20C; Salmonids present.

TCAP = 25C; Salmonids absent.

g. Shall not exceed the numerical value

given by: ((~~0.80~~

~~----------~~

~~(FT)(FPH)(RATIO)~~))

0.80 (FT)(FPH)(RATIO)

where: RATIO = ((~~16~~)) 13.5 ; 7.7 pH 9

RATIO = ((~~24 x 10$^{(7.7-pH)}$~~))

(20.25 x 10$^{(7.7-pH)}$) (1 + 10$^{(7.4-pH)}$) ; 6.5 pH 7.7

((~~----------~~

~~$1+10^{(7.4-pH)}$~~))

where: FT and FPH are as shown in (f) above except:

TCAP = 15C; Salmonids present.

TCAP = 20C; Salmonids absent.

h. Measured in milligrams per liter rather than micrograms per liter.

i. ((~~$(0.865)(e^{(1.128[ln(hardness)]-3.828)})$~~))

$(0.944)(e^{(1.128[In(hardness)]-3.828)})$ at hardness = 100. Conversion factor (CF) of 0.944 is hardness dependent. CF is calculated for other hardnesses as follows: CF = 1.136672 - [(In hardness)(0.041838)].

j. ((~~$(0.865)(e^{(0.7852[ln(hardness)]-3.490)})$~~)) $(0.909)(e^{(0.7852[In(hardness)]-3.490)})$ at hardness = 100. Conversions factor (CF) of 0.909 is hardness dependent. CF is calculated for other hardnesses as follows: CF = 1.101672 - [(In hardness)(0.041838)].

k. Criterion based on dissolved chloride in association with sodium. This criterion probably will not be adequately protective when the chloride is associated with potassium, calcium, or magnesium, rather than sodium.

l. Salinity dependent effects. At low salinity the 1-hour average may not be sufficiently protective.

m. $(0.316)e^{(0.8190[ln(hardness)] +3.688)}$

n. $(0.860)e^{(0.8190[ln(hardness)] +1.561)}$

o. ((~~(0.862)~~)) $(0.960)(e^{(0.9422[ln(hardness)] -1.464)})$

p. ((~~(0.862)~~)) $(0.960)(e^{(0.8545[ln(hardness)] -1.465)})$

q. ((~~$(0.687)(e^{(1.273[ln(hardness)] -1.460)})$~~)) $(0.791)(e^{(1.273[In(hardness)] -1.460)})$ at hardness = 100. Conversion factor (CF) of 0.791 is hardness dependent. CF is calculated for other hardnesses as follows: CF = 1.46203 - [(In hardness)(0.145712)].

r. ((~~$(0.687)(e^{(1.273[ln(hardness)] -4.705)})$~~)) $(0.791)(e^{(1.273[In(hardness)] -4.705)})$ at hardness = 100. Conversion factor (CF) of 0.791 is hardness dependent. CF is calculated for other hardnesses as follows: CF = 1.46203 - [(In hardness)(0.145712)].

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s. If the four-day average chronic concentration is exceeded more than once in a three-year period, the edible portion of the consumed species should be analyzed. Said edible tissue concentrations shall not be allowed to exceed 1.0 mg/kg of methylmercury.

t. ((~~(0.95)~~)) (0.998)($e^{(0.8460[\ln(\text{hardness})] + 3.3612)}$)

u. ((~~(0.95)~~)) (0.997)($e^{(0.8460[\ln(\text{hardness})] + 1.1645)}$)

v. $e^{[1.005(\text{pH}) - 5.290]}$

w. $e^{[1.005(\text{pH}) - 4.830]}$

x. The status of the fish community should be monitored whenever the concentration of selenium exceeds 5.0 ug/1 in salt water.

y. ((~~(0.531)~~)) (0.85)($e^{(1.72[\ln(\text{hardness})] - 6.52)}$)

z. Channel Catfish may be more acutely sensitive.

aa. ((~~(0.891)~~)) (0.978)($e^{(0.8473[\ln(\text{hardness})] + 0.8604)}$)

bb. ((~~(0.891)~~)) (0.986)($e^{(0.8473[\ln(\text{hardness})] + 0.7614)}$)

cc. Nonlethal effects (growth, C-14 uptake, and chlorophyll production) to diatoms *(Thalassiosira aestivalis* and *Skeletonema costatum)* which are common to Washington's waters have been noted at levels below the established criteria. The importance of these effects to the diatom populations and the aquatic system is sufficiently in question to persuade the state to adopt the USEPA National Criteria value (36 g/L) as the state threshold criteria, however, wherever practical the ambient concentrations should not be allowed to exceed a chronic marine concentration of 21 g/L.

dd. These ambient criteria in the table are ((~~based on~~)) for the dissolved fraction ((~~(for cyanide criteria using the weak and dissociable method) of the metal. The department shall apply the criteria as total recoverable values to calculate effluent limits unless data is made available to the department clearly demonstrating the seasonal partitioning of the dissolved metal in the ambient water in relation to an effluent discharge~~)). The cyanide criteria are based on the weak acid dissociable method. The metals criteria may not be used to calculate total recoverable effluent limits unless the seasonal partitioning of the dissolved to total metals in the ambient water are known. When this information is absent, these metals criteria shall be applied as total recoverable values, determined by back-calculation, using the conversion factors incorporated in the criterion equations. Metals criteria may be adjusted on a site-specific basis when data ((~~is~~)) are made

available to the department clearly demonstrating the effective use of the water effects ratio approach established by USEPA, as generally guided by the procedures in USEPA *Water Quality Standards Handbook,* December 1983, as supplemented or replaced. Information which is used to develop effluent limits based on applying metals partitioning studies or the water effects ratio approach shall be identified in the permit fact sheet developed pursuant to WAC 173-220-060 or 173-226-110, as appropriate, and shall be made available for the public comment period required pursuant to WAC 173-220-050 or 173-226-130(3), as appropriate.

ee. The criteria for cyanide is based on the weak and dissociable method in the 17th Ed. *Standard Methods for the Examination of Water and Wastewater*, 4500-CN I, and as revised (see footnote dd, above).

ff. These criteria are based on the total-recoverable fraction of the metal.

gg. Where methods to measure trivalent chromium are unavailable, these criteria are to be represented by total-recoverable chromium.

hh. Tables for the conversion of total ammonia to un-ionized ammonia for freshwater can be found in the USEPA's *Quality Criteria for Water*, 1986. Criteria concentrations based on total ammonia for marine water can be found in USEPA *Ambient Water Quality Criteria for Ammonia (Saltwater)-1989*, EPA440/5-88-004, April 1989.

ii. Conversion factor to calculate dissolved metal concentration is 0.982.

jj. Conversion factor to calculate dissolved metal concentration is 0.962.

kk. Conversion factor to calculate dissolved metal concentration is 0.85.

ll. Marine conversion factors (CF) used for calculating dissolved metals concentrations. Conversion factors are applicable to both acute and chronic criteria for all metals except mercury. CF for mercury is applicable to the acute criterion only. Conversion factors are already incorporated into the criteria in the table. Dissolved criterion = criterion x CF

Metal CF

Arsenic 1.000

Cadmium 0.994

Chromium (VI) 0.993

Copper 0.83

Lead 0.951

Mercury 0.85

Nickel 0.990

Selenium 0.998

Silver 0.85

Zinc 0.946

mm. The cyanide criteria are: 9.1g/l chronic and 2.8g/l acute and are applicable only to waters which are east of a line from Point Roberts to Lawrence Point, to Green Point to Deception Pass; and south from Deception Pass and of a line from Partridge Point to Point Wilson.

(4) *USEPA Quality Criteria for Water, 1986* shall be used in the use and interpretation of the values listed in subsection ((~~(1)~~)) (3) of this section.

(5) Concentrations of toxic, and other substances with toxic propensities not listed in subsection ((~~(1)~~)) (3) of this section shall be determined in consideration of *USEPA Quality Criteria for Water, 1986,* and as revised, and other relevant information as appropriate. Human health-based water quality criteria used by the state are contained in 40 CFR 131.36 (known as the National Toxics Rule).

(6) Risk-based criteria for carcinogenic substances shall be selected such that the upper-bound excess cancer risk is less than or equal to one in one million.

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-040, filed 11/25/92, effective 12/26/92.]

NOTES:

Reviser's note: The brackets and enclosed material in the text of the above section occurred in the copy filed by the agency.

Reviser's note: The brackets and enclosed material in the text of the above section occurred in the copy filed by the agency and appear in the Register pursuant to the requirements of RCW 34.08.040.

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-050 Radioactive substances. (1) Deleterious concentrations of radioactive materials for all classes shall be as determined by the lowest practicable concentration attainable and in no case shall exceed:

(a) ((~~1/100~~)) 1/12.5 of the values listed in WAC 246-221-290 (Column 2, Table II, ((~~Appendix A~~)) effluent concentrations, rules and regulations for radiation protection); or

(b) USEPA Drinking Water Regulations for radionuclides, as published in the Federal Register of July 9, 1976, or subsequent revisions thereto.

(2) Nothing in this chapter shall be interpreted to be applicable to those aspects of governmental regulation of radioactive waters which have been preempted from state regulation by the Atomic Energy Act of 1954, as amended, as interpreted by the United States Supreme Court in the cases of *Northern States Power Co. v. Minnesota 405 U.S. 1035 (1972) and Train v. Colorado Public Interest Research Group, 426 U.S. 1 (1976).*

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-050, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-060 General considerations. The following general guidelines shall apply to the water quality criteria and classifications set forth in WAC 173-201A-030 through 173-201A-140 hereof:

(1) At the boundary between waters of different classifications, the water quality criteria for the higher classification shall prevail.

(2) In brackish waters of estuaries, where the fresh and marine water quality criteria differ within the same classification, the criteria shall be ((~~interpolated on the basis of salinity; except that the marine water quality criteria shall apply for dissolved oxygen when the salinity is one part per thousand or greater and for fecal coliform organisms when the salinity is ten parts per thousand or greater~~)) applied on the basis of vertically averaged salinity. The freshwater criteria shall be applied at any point where ninety-five percent of the vertically averaged daily maximum salinity values are less than or equal to one part per thousand. Marine

criteria shall apply at all other locations; except that the marine water quality criteria shall apply for dissolved oxygen when the salinity is one part per thousand or greater and for fecal coliform organisms when the salinity is ten parts per thousand or greater.

(3) In determining compliance with the fecal coliform criteria in WAC 173-201A-030, averaging of data collected beyond a thirty-day period, or beyond a specific discharge event under investigation, shall not be permitted when such averaging would skew the data set so as to mask noncompliance periods.

(4)(a) The water quality criteria herein established for total dissolved gas shall not apply when the stream flow exceeds the seven-day, ten-year frequency flood.

(b) The total dissolved gas criteria may be adjusted to aid fish passage over hydroelectric dams when consistent with a department approved gas abatement plan. This gas abatement plan must be accompanied by fisheries management and physical and biological monitoring plans. The elevated total dissolved gas levels are intended to allow increased fish passage without causing more harm to fish populations than caused by turbine fish passage. The specific allowances for total dissolved gas exceedances are listed as special conditions for sections of the Snake and Columbia rivers in WAC 173-201A-130 and as shown in the following exemption:

Special fish passage exemption for sections of the Snake and Columbia rivers: When spilling water at dams is necessary to aid fish passage, total dissolved gas must not exceed an average of one hundred fifteen percent as measured at Camas/Washougal below Bonneville dam or as measured in the forebays of the next downstream dams. Total dissolved gas must also not exceed an average of one hundred twenty percent as measured in the tailraces of each dam. These averages are based on the twelve highest hourly readings in any one day of total dissolved gas. In addition, there is a maximum total dissolved gas one hour average of one hundred twenty-five percent, relative to atmospheric pressure, during spillage for fish passage. These special conditions for total dissolved gas in the Snake and Columbia rivers are viewed as temporary and are to be reviewed by the year 2003.

(c) Nothing in these special conditions allows an impact to existing and characteristic uses.

(5) Waste discharge permits, whether issued pursuant to the National Pollutant Discharge Elimination System or otherwise, shall be conditioned so the discharges authorized will meet the water quality standards.

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(a) However, persons discharging wastes in compliance with the terms and conditions of permits shall not be subject to civil and criminal penalties on the basis that the discharge violates water quality standards.

(b) Permits shall be subject to modification by the department whenever it appears to the department the discharge violates water quality standards. Modification of permits, as provided herein, shall be subject to review in the same manner as originally issued permits.

(6) No waste discharge permit shall be issued which results in a violation of established water quality criteria, except as provided for under WAC 173-201A-100 or 173-201A-110.

(7) Due consideration will be given to the precision and accuracy of the sampling and analytical methods used as well as existing conditions at the time, in the application of the criteria.

(8) The analytical testing methods for these criteria shall be in accordance with the *"Guidelines Establishing Test Procedures for the Analysis of Pollutants" (40 C.F. R. Part 136)* and other or superseding methods published and/or approved by the department following consultation with adjacent states and concurrence of the USEPA.

(9) Nothing in this chapter shall be interpreted to prohibit the establishment of effluent limitations for the control of the thermal component of any discharge in accordance with Section 316 of the federal Clean Water Act (33 U.S.C. 1251 et seq.).

(10) The primary means for protecting water quality in wetlands is through implementing the antidegradation procedures section (WAC 173-201A-070).

(a) In addition to designated uses, wetlands may have existing beneficial uses that are to be protected that include ground water exchange, shoreline stabilization, and storm water attenuation.

(b) Water quality in wetlands is maintained and protected by maintaining the hydrologic conditions, hydrophytic vegetation, and substrate characteristics necessary to support existing and designated uses.

(c) Wetlands shall be delineated using the Washington State Wetlands Identification and Delineation Manual, in accordance with WAC 173-22-035.

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-060, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-110 Short-term modifications. ((~~(1)~~)) The criteria and special conditions established in WAC 173-201A-030 through 173-201A-140 may be modified for a specific water body on a short- basis when necessary to accommodate essential activities, respond to emergencies, or to otherwise protect the public interest, even though such activities may result in a temporary reduction of water quality conditions below those criteria and classifications established by this regulation. ((~~Such modification shall be issued in writing by the director or his/her designee subject to such terms and conditions as he/she may prescribe, and such modification shall not exceed a twelve-month period.~~

~~(2)~~)) Such activities must be conditioned, timed, and restricted (i.e., hours or days rather than weeks or months) in a manner that will minimize water quality degradation to existing and characteristic uses. In no case will any degradation of water quality be allowed if this degradation significantly interferes with or becomes injurious to ((~~existing~~)) characteristic water uses or causes long-term harm to the environment.

((~~(3) Notwithstanding the above, the aquatic application of herbicides which result in water use restrictions shall be considered an activity for which a short-term modification generally may be issued subject to the following conditions:~~

~~(a)~~)) (1) A short-term modification may be issued in writing by the director or his/her designee to an individual or entity proposing the aquatic application of pesticides, including but not limited to those used for control of federally or state listed noxious and invasive species, and excess populations of native aquatic plants, mosquitoes, burrowing shrimp, and fish, subject to the following terms and conditions:

(a) A short-term modification will in no way lessen or remove the project proponent's obligations and liabilities under other federal, state and local rules and regulations.

(b) A request for a short-term modification shall be made to the department on forms supplied by the department. Such request ((~~generally~~)) shall be made at least thirty days prior to ((~~herbicide application;~~

~~(b) Such herbicide application shall be in accordance with state of Washington department of agriculture regulations;~~

~~(c) Such herbicide application shall be in accordance with label provisions promulgated by USEPA under the federal Insecticide, Fungicide, and Rodenticide Act, as amended (7 U.S.C. 136, et seq.);~~

~~(d) Notice, including identification of the herbicide, applicator, location where the herbicide will be applied, proposed timing and method of application, and water use restrictions shall be given according to the following requirements:~~

~~(i) Appropriate public notice as determined and prescribed by the director or his/her designee shall be given of any water use restrictions specified in USEPA label provisions;~~

~~(ii) The appropriate regional offices of the departments of fisheries and wildlife shall be notified twenty-four hours prior to herbicide application; and~~

~~(iii) In the event of any fish kills, the departments of ecology, fisheries, and wildlife shall be notified immediately~~)) initiation of the proposed activity, and after the project proponent has complied with the requirements of the State Environmental Policy Act (SEPA);

(c) A short-term modification shall be valid for the duration of the activity requiring modification of the criteria and special conditions in WAC 173-201A-030 through 173-201A-140, or for one year, whichever is less. Ecology may authorize a longer duration where the activity is part of an ongoing or long-term operation and maintenance plan, integrated pest or noxious weed management plan, waterbody or watershed management plan, or restoration plan. Such a plan must be developed through a public involvement process consistent with the Administrative Procedure Act (chapter 34.05 RCW) and be in compliance with SEPA, chapter 43.21C RCW, in which case the standards may be modified for the duration of the plan, or for five years, whichever is less;

(d) Appropriate public notice as determined and prescribed by the director or his/her designee shall be given, identifying the pesticide, applicator, location where the pesticide will be applied, proposed timing and method of application, and any water use restrictions specified in USEPA label provisions;

(e) The ((~~herbicide~~)) pesticide application shall be made at times so as to:

(i) Minimize public water use restrictions during weekends; and

(ii) ((~~Completely~~)) Avoid public water use restrictions during the opening week of fishing season, Memorial Day weekend, Independence Day weekend, and Labor Day weekend;

(f) Any additional conditions as may be prescribed by the director or his/her designee.

(2) A short-term modification may be issued for the control or eradication of noxious weeds identified as such in accordance with the state noxious weed control law, chapter 17.10 RCW, and Control of spartina and purple loosestrife, chapter 17.26 RCW. Short-term modifications for noxious weed control shall be included in a water quality permit issued in accordance with RCW 90.48.445, and the following requirements:

(a) Water quality permits for noxious weed control may be issued to the Washington state department of agriculture (WSDA) for the purposes of coordinating and conducting noxious weed control activities consistent with their responsibilities under chapter 17.10 and 17.26 RCW. Coordination may include noxious weed control activities identified in a WSDA integrated noxious weed management plan and conducted by individual landowners or land managers.

(b) Water quality permits may also be issued to individual landowners or land managers for noxious weed control activities where such activities are not covered by a WSDA integrated noxious weed management plan.

(3) The turbidity criteria established under WAC 173-201A-030 shall be modified to allow a temporary mixing zone during and immediately after necessary in-water or shoreline construction activities that result in the disturbance of in-place sediments. A temporary turbidity mixing zone is subject to the constraints of WAC 173-201A-100 (4) and (6) and is authorized only after the activity has received all other necessary local and state permits and approvals, and after the implementation of appropriate best management practices to avoid or minimize disturbance of in-place sediments and exceedances of the turbidity criteria. A temporary turbidity mixing zone shall be as follows:

(a) For waters up to 10 cfs flow at the time of construction, the point of compliance shall be one hundred feet downstream from activity causing the turbidity exceedance.

(b) For waters above 10 cfs up to 100 cfs flow at the time of construction, the

point of compliance shall be two hundred feet downstream of activity causing the turbidity exceedance.

(c) For waters above 100 cfs flow at the time of construction, the point of compliance shall be three hundred feet downstream of activity causing the turbidity exceedance.

(d) For projects working within or along lakes, ponds, wetlands, estuaries, marine waters or other nonflowing waters, the point of compliance shall be at a radius of one hundred fifty feet from activity causing the turbidity exceedance.

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-110, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-130 Specific classifications--Freshwater. Specific fresh surface waters of the state of Washington are classified as follows:

(1) American River. Class AA

(2) Big Quilcene River and tributaries. Class AA

(3) Bumping River. Class AA

(4) Burnt Bridge Creek. Class A

(5) Cedar River from Lake Washington to the Maplewood Bridge (river mile 4.1). Class A

(6) Cedar River and tributaries from the Maplewood Bridge (river mile 4.1) to Landsburg Dam (river mile 21.6). Class AA

(7) Cedar River and tributaries from Landsburg Dam (river mile 21.6) to headwaters. Special condition - no waste discharge will be permitted. Class AA

(8) Chehalis River from upper boundary of Grays Harbor at Cosmopolis (river mile 3.1, longitude 12345'45" W) to Scammon Creek (river mile 65.8). Class A

(9) Chehalis River from Scammon Creek (river mile 65.8) to Newaukum River (river mile 75.2). Special condition - dissolved oxygen shall exceed 5.0 mg/L from June 1 to September 15. For the remainder of the year, the dissolved oxygen shall meet Class A

criteria. Class A

(10) Chehalis River from Newaukum River (river mile 75.2) to Rock Creek (river mile 106.7). Class A

(11) Chehalis River, from Rock Creek (river mile 106.7) to headwaters. Class AA

(12) Chehalis River, south fork. Class A

(13) Chewuch River. Class AA

(14) Chiwawa River. Class AA

(15) Cispus River. Class AA

(16) Clearwater River. Class A

(17) Cle Elum River. Class AA

(18) Cloquallum Creek. Class A

(19) Clover Creek from outlet of Lake Spanaway to inlet of Lake Steilacoom. Class A

(20) Columbia River from mouth to the Washington-Oregon border (river mile 309.3). Special conditions - temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed 0.3C due to any single source or 1.1C due to all such activities combined. Dissolved oxygen shall exceed 90 percent of saturation. Special condition - special fish passage exemption as described in WAC 173-201A-060 (4)(b). Class A

(21) Columbia River from Washington-Oregon border (river mile 309.3) to Grand Coulee Dam (river mile 596.6). Special condition from Washington-Oregon border (river mile 309.3) to Priest Rapids Dam (river mile 397.1). Temperaturell not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Special condition - special fish passage exemption as described in WAC 173-201A-060 (4)(b). Class A

(22) Columbia River from Grand Coulee Dam (river mile 596.6) to Canadian border (river mile 745.0). Class AA

(23) Colville River. Class A

(24) Coweeman River from mouth to Mulholland Creek (river mile 18.4). Class A

(25) Coweeman River from Mulholland Creek (river mile 18.4) to headwaters. Class AA

(26) Cowlitz River from mouth to base of Riffe Lake Dam (river mile 52.0). Class A

(27) Cowlitz River from base of Riffe Lake Dam (river mile 52.0) to headwaters. Class AA

(28) Crab Creek and tributaries. Class B

(29) Decker Creek. Class AA

(30) Deschutes River from mouth to boundary of Snoqualmie National Forest (river mile 48.2). Class A

(31) Deschutes River from boundary of Snoqualmie National Forest (river mile 48.2) to headwaters. Class AA

(32) Dickey River. Class A

(33) Dosewallips River and tributaries. Class AA

(34) Duckabush River and tributaries. Class AA

(35) Dungeness River from mouth to Canyon Creek (river mile 10.8). Class A

(36) Dungeness River and tributaries from Canyon Creek (river mile 10.8) to headwaters. Class AA

(37) Duwamish River from mouth south of a line bearing 254 true from the NW corner of berth 3, terminal No. 37 to the Black River (river mile 11.0) (Duwamish River continues as the Green River above the Black River). Class B

(38) Elochoman River. Class A

(39) Elwha River and tributaries. Class AA

(40) Entiat River from Wenatchee National Forest boundary (river mile 20.5) to headwaters. Class AA

(41) Grande Ronde River from mouth to Oregon border (river mile 37). Special condition - temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Class A

(42) Grays River from Grays River Falls (river mile 15.8) to headwaters. Class AA

(43) Green River (Cowlitz County). Class AA

(44) Green River (King County) from Black River (river mile 11.0 and point where Duwamish River continues as the Green River) to west boundary of Sec. 27-T21N-R6E (west boundary of Flaming Geyser State Park at river mile 42.3). Class A

(45) Green River (King County) from west boundary of Sec. 27-T21N-R6E (west boundary of Flaming Geyser State Park, river mile 42.3) to west boundary of Sec. 13-T21N-R7E (river mile 59.1). Class AA

(46) Green River and tributaries (King County) from west boundary of Sec. 13-T21N-R7E (river mile 59.1) to headwaters. Special condition - no waste discharge will be permitted. Class AA

(47) Hamma Hamma River and tributaries. Class AA

(48) Hanaford Creek from mouth to east boundary of Sec. 25-T15N-R2W (river mile 4.1). Special condition - dissolved oxygen shall exceed 6.5 mg/L. Class A

(49) Hanaford Creek from east boundary of Sec. 25-T15N-R2W (river mile 4.1) to headwaters. Class A

(50) Hoh River and tributaries. Class AA

(51) Hoquiam River (continues as west fork above east fork) from mouth to river mile 9.3 (Dekay Road Bridge) (upper limit of tidal influence). Class B

(52) Humptulips River and tributaries from mouth to Olympic National Forest boundary on east fork (river mile 12.8) and west fork (river mile 40.4) (main stem continues as west fork). Class A

(53) Humptulips River, east fork from Olympic National Forest boundary (river mile 12.8) to headwaters. Class AA

(54) Humptulips River, west fork from Olympic National Forest boundary (river mile 40.4)

to headwaters. Class AA

(55) Issaquah Creek. Class A

(56) Kalama River from lower Kalama River Falls (river mile 10.4) to headwaters. Class AA

(57) Klickitat River from Little Klickitat River (river mile 19.8) to boundary of Yakima Indian Reservation. Class AA

(58) Lake Washington Ship Canal from Government Locks (river mile 1.0) to Lake Washington (river mile 8.6). Special condition - salinity shall not exceed one part per thousand (1.0 ppt) at any point or depth along a line that transects the ship canal at the University Bridge (river mile 6.1). Lake Class

(59) Lewis River, east fork, from Multon Falls (river mile 24.6) to headwaters. Class AA

(60) Little Wenatchee River. Class AA

(61) Methow River from mouth to Chewuch River (river mile 50.1). Class A

(62) Methow River from Chewuch River (river mile 50.1) to headwaters. Class AA

(63) Mill Creek from mouth to 13th Street Bridge in Walla Walla (river mile 6.4). Special condition - dissolved oxygen concentration shall exceed 5.0 mg/L. Class B

(64) Mill Creek from 13th Street Bridge in Walla Walla (river mile 6.4) to Walla Walla Waterworks Dam ((~~(river mile 25.2)~~)) (river mile 11.5). Class A

(65) Mill Creek and tributaries from city of Walla Walla Waterworks Dam ((~~(river mile 25.2)~~)) (river mile 21.6) to headwaters. Special condition - no waste discharge will be permitted. Class AA

(66) Naches River from Snoqualmie National Forest boundary (river mile 35.7) to headwaters. Class AA

(67) Naselle River from Naselle "Falls" (cascade at river mile 18.6) to headwaters. Class AA

(68) Newaukum River. Class A

(69) Nisqually River from mouth to Alder Dam (river mile 44.2). Class A

(70) Nisqually River from Alder Dam (river mile 44.2) to headwaters. Class AA

(71) Nooksack River from mouth to Maple Creek (river mile 49.7). Class A

(72) Nooksack River from Maple Creek (river mile 49.7) to headwaters. Class AA

(73) Nooksack River, south fork, from mouth to Skookum Creek (river mile 14.3). Class A

(74) Nooksack River, south fork, from Skookum Creek (river mile 14.3) to headwaters. Class AA

(75) Nooksack River, middle fork. Class AA

(76) Okanogan River. Class A

(77) Palouse River from mouth to south fork (Colfax, river mile 89.6). Class B

(78) Palouse River from south fork (Colfax, river mile 89.6) to Idaho border (river mile 123.4). Special condition - temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Class A

(79) Pend Oreille River from Canadian border (river mile 16.0) to Idaho border (river mile 87.7). Special condition - temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Class A

(80) Pilchuck River from city of Snohomish Waterworks Dam (river mile 26.8) to headwaters. Class AA

(81) Puyallup River from mouth to river mile 1.0. Class B

(82) Puyallup River from river mile 1.0 to Kings Creek (river mile 31.6). Class A

(83) Puyallup River from Kings Creek (river mile 31.6) to headwaters. Class AA

(84) Queets River and tributaries. Class AA

(85) Quillayute River. Class AA

(86) Quinault River and tributaries. Class AA

(87) Salmon Creek (Clark County). Class A

(88) Satsop River from mouth to west fork (river mile 6.4). Class A

(89) Satsop River, east fork. Class AA

(90) Satsop River, middle fork. Class AA

(91) Satsop River, west fork. Class AA

(92) Skagit River from mouth to Skiyou Slough-lower end (river mile 25.6). Class A

(93) Skagit River and tributaries (includes Baker, Suak, Suiattle, and Cascade rivers) from Skiyou Slough-lower end, (river mile 25.6) to Canadian border (river mile 127.0). Special condition - Skagit River (Gorge by-pass reach) from Gorge Dam (river mile 96.6) to Gorge Powerhouse (river mile 94.2). Temperature shall not exceed 21C due to human activities. When natural conditions exceed 21C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C, nor shall such temperature increases, at any time, exceed t=34/(T+9). Class AA

(94) Skokomish River and tributaries. Class AA

(95) Skookumchuck River from Bloody Run Creek (river mile 21.4) to headwaters. Class AA

(96) Skykomish River from mouth to May Creek (above Gold Bar at river mile 41.2). Class A

(97) Skykomish River from May Creek (above Gold Bar at river mile 41.2) to headwaters. Class AA

(98) Snake River from mouth to Washington-Idaho-Oregon border (river mile 176.1). Special condition:

(a) Below Clearwater River (river mile 139.3). Temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Special condition - special fish passage exemption as described in WAC 173-201A-060 (4)(b).

(b) Above Clearwater River (river mile 139.3). Temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increases will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed 0.3C due to any single source or 1.1C due to all such activities combined. Class A

(99) Snohomish River from mouth and east of longitude 12213'40"W upstream to latitude 4756'30"N (southern tip of Ebey Island at river mile 8.1). Special condition - fecal coliform organism levels shall both not exceed a geometric mean value of 200 colonies/100 mL and not have more than 10 percent of the samples obtained for calculating the mean value exceeding 400 colonies/100 mL. Class A

(100) Snohomish River upstream from latitude 4756'30"N (southern tip of Ebey Island river mile 8.1) to confluence with Skykomish and Snoqualmie River (river mile 20.5). Class A

(101) Snoqualmie River and tributaries from mouth to west boundary of Twin Falls State Park on south fork (river mile 9.1). Class A

(102) Snoqualmie River, middle fork. Class AA

(103) Snoqualmie River, north fork. Class AA

(104) Snoqualmie River, south fork, from west boundary of Twin Falls State Park (river mile 9.1) to headwaters. Class AA

(105) Soleduck River and tributaries. Class AA

(106) Spokane River from mouth to Long Lake Dam (river mile 33.9). Special condition - temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed $t=34/(T+9)$. Class A

(107) Spokane River from Long Lake Dam (river mile 33.9) to Nine Mile Bridge (river mile 58.0). Special conditions:

(a) The average euphotic zone concentration of total phosphorus (as P) shall not exceed 25g/L during the period of June 1 to October 31.

(b) Temperature shall not exceed 20.0C, due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases,

at any time exceed t=34/(T+9). Lake Class

(108) Spokane River from Nine Mile Bridge (river mile 58.0) to the Idaho border (river mile 96.5). Temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time exceed t=34/(T+9). Class A

(109) Stehekin River. Class AA

(110) Stillaguamish River from mouth to north and south forks (river mile 17.8). Class A

(111) Stillaguamish River, north fork, from mouth to Squire Creek (river mile 31.2). Class A

(112) Stillaguamish River, north fork, from Squire Creek (river mile 31.2) to headwaters. Class AA

(113) Stillaguamish River, south fork, from mouth to Canyon Creek (river mile 33.7). Class A

(114) Stillaguamish River, south fork, from Canyon Creek (river mile 33.7) to headwaters. Class AA

(115) Sulphur Creek. Class B

(116) Sultan River from mouth to Chaplain Creek (river mile 5.9). Class A

(117) Sultan River and tributaries from Chaplain Creek (river mile 5.9) to headwaters. Special condition - no waste discharge will be permitted above city of Everett Diversion Dam (river mile 9.4). Class AA

(118) Sumas River from Canadian border (river mile 12) to headwaters (river mile 23). Class A

(119) Tieton River. Class AA

(120) Tolt River, south fork and tributaries from mouth to west boundary of Sec. 31-T26N-R9E (river mile 6.9). Class AA

(121) Tolt River, south fork from west boundary of Sec. 31-T26N-R9E (river mile 6.9) to headwaters. Special condition - no waste discharge will be permitted. Class AA

(122) Touchet River, north fork from Dayton water intake structure (river mile 3.0) to headwaters. Class AA

(123) Toutle River, north fork, from Green River to headwaters. Class AA

(124) Toutle River, south fork. Class AA

(125) Tucannon River from Umatilla National Forest boundary (river mile 38.1) to headwaters. Class AA

(126) Twisp River. Class AA

(127) Union River and tributaries from Bremerton Waterworks Dam (river mile 6.9) to headwaters. Special condition - no waste discharge will be permitted. Class AA

(128) Walla Walla River from mouth to Lowden (Dry Creek at river mile 27.2). Class B

(129) Walla Walla River from Lowden (Dry Creek at river mile 27.2) to Oregon border (river mile 40). Special condition - temperature shall not exceed 20.0C due to human activities. When natural conditions exceed 20.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Class A

(130) Wenatchee River from Wenatchee National Forest boundary (river mile 27.1) to headwaters. Class AA

(131) White River (Pierce-King counties) from Mud Mountain Dam (river mile 27.1) to headwaters. Class AA

(132) White River (Chelan County). Class AA

(133) Wildcat Creek. Class A

(134) Willapa River upstream of a line bearing 70 true through Mailboat Slough light (river mile 1.8). Class A

(135) Wishkah River from mouth to river mile 6 (SW 1/4 SW 1/4 NE 1/4 Sec. 21-T18N-R9W). Class B

(136) Wishkah River from river mile 6 (SW 1/4 SW 1/4 NE 1/4 Sec. 21-T18N-R9W) to west fork (river mile 17.7). Class A

(137) Wishkah River from west fork of Wishkah River (river mile 17.7) to south boundary of Sec. 33-T21N-R8W (river mile 32.0). Class AA

(138) Wishkah River and tributaries from south boundary of Sec. 33-T21N-R8W (river mile 32.0) to headwaters. Special condition - no waste discharge will be permitted. Class AA

(139) Wynoochee River from mouth to Olympic National Forest boundary (river mile 45.9). Class A

(140) Wynoochee River from Olympic National Forest boundary (river mile 45.9) to headwaters. Class AA

(141) Yakima River from mouth to Cle Elum River (river mile 185.6). Special condition - temperature shall not exceed 21.0C due to human activities. When natural conditions exceed 21.0C, no temperature increase will be allowed which will raise the receiving water temperature by greater than 0.3C; nor shall such temperature increases, at any time, exceed t=34/(T+9). Class A

(142) Yakima River from Cle Elum River (river mile 185.6) to headwaters. Class AA

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-130, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-140 Specific classifications--Marine water. Specific marine surface waters of the state of Washington are classified as follows:

(1) Budd Inlet south of latitude 4704'N (south of Priest Point Park). Class B

(2) Coastal waters: Pacific Ocean from Ilwaco to Cape Flattery. Class AA

(3) Commencement Bay south and east of a line bearing 258 true from "Brown's Point" and north and west of line bearing 225 true through the Hylebos waterway light. Class A

(4) Commencement Bay, inner, south and east of a line bearing 225 true through Hylebos waterway light except the city waterway south and east of south 11th Street. Class B

(5) Commencement Bay, city waterway south and east of south 11th Street. Class C

(6) Drayton Harbor, south of entrance. Class A

(7) Dyes and Sinclair Inlets west of longitude 12237'W. Class A

(8) Elliott Bay east of a line between Pier 91 and Duwamish head. Class A

(9) Everett Harbor, inner, northeast of a line bearing 121 true from approximately 4759'5"N and 12213'44"W (southwest corner of the pier). Class B

(10) Grays Harbor west of longitude 12359'W. Class A

(11) Grays Harbor east of longitude 12359'W to longitude 12345'45"W (Cosmopolis Chehalis River, river mile 3.1). Special condition - dissolved oxygen shall exceed 5.0 mg/L. Class B

(12) Guemes Channel, Padilla, Samish and Bellingham Bays east of longitude 12239'W and north of latitude 4827'20"N. Class A

(13) Hood Canal. Class AA

(14) Mukilteo and all North Puget Sound west of longitude 12239' W (Whidbey, Fidalgo, Guemes and Lummi islands and State Highway 20 Bridge at Deception Pass), except as otherwise noted. Class AA

(15) Oakland Bay west of longitude 12305'W (inner Shelton harbor). Class B

(16) Port Angeles south and west of a line bearing 152 true from buoy "2" at the tip of Ediz Hook. Class A

(17) Port Gamble south of latitude ((~~4715'20"N~~)) 4751'20"N. Class A

(18) Port Townsend west of a line between Point Hudson and Kala Point. Class A

(19) Possession Sound, south of latitude 4757'N. Class AA

(20) Possession Sound, Port Susan, Saratoga Passage, and Skagit Bay east of Whidbey Island and State Highway 20 Bridge at Deception Pass between latitude 4757'N (Mukilteo) and latitude 4827'20"N (Similk Bay), except as otherwise noted. Class A

(21) Puget Sound through Admiralty Inlet and South Puget Sound, south and west to longitude 12252'30"W (Brisco Point) and longitude 12251'W (northern tip of Hartstene Island). Class AA

(22) Sequim Bay southward of entrance. Class AA

(23) South Puget Sound west of longitude 12252'30"W (Brisco Point) and longitude 12251'W (northern tip of Hartstene Island, except as otherwise noted). Class A

(24) Strait of Juan de Fuca. Class AA

(25) Totten Inlet and Little Skookum Inlet, west of longitude ((~~1225'32"~~)) 12256'32" (west side of Steamboat Island). Class AA

(26) Willapa Bay seaward of a line bearing 70 true through Mailboat Slough light (Willapa River, river mile 1.8). Class A

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-140, filed 11/25/92, effective 12/26/92.]

AMENDATORY SECTION (Amending Order 92-29, filed 11/25/92, effective 12/26/92)

WAC 173-201A-160 Implementation. (1) **Discharges from municipal, commercial, and industrial operations.** The primary means to be used for controlling municipal, commercial, and industrial waste discharges shall be through the issuance of waste disposal permits, as provided for in RCW 90.48.160, 90.48.162, and 90.48.260.

(2) **Miscellaneous waste discharge or water quality effect sources.** The director shall, through the issuance of regulatory permits, directives, and orders, as are appropriate, control miscellaneous waste discharges and water quality effect sources not covered by subsection (1) of this section.

(3) **Nonpoint source and storm water pollution.**

(a) Activities which generate nonpoint source pollution shall be conducted so as to comply with the water quality standards. The primary means to be used for requiring compliance with the standards shall be through best management practices required in waste discharge permits, rules, orders, and directives issued by the department for activities which generate nonpoint source pollution.

(b) Best management practices shall be applied so that when all appropriate combinations of individual best management practices are utilized, violation of water quality criteria shall be prevented. If a discharger is applying all best

management practices appropriate or required by the department and a violation of water quality criteria occurs, the discharger shall modify existing practices or apply further water pollution control measures, selected or approved by the department, to achieve compliance with water quality criteria. Best management practices established in permits, orders, rules, or directives of the department shall be reviewed and modified, as appropriate, so as to achieve compliance with water quality criteria.

(c) Activities which contribute to nonpoint source pollution shall be conducted utilizing best management practices to prevent violation of water quality criteria. When applicable best management practices are not being implemented, the department may conclude individual activities are causing pollution in violation of RCW 90.48.080. In these situations, the department may pursue orders, directives, permits, or civil or criminal sanctions to gain compliance with the standards.

(d) Activities which cause pollution of storm water shall be conducted so as to comply with the water quality standards. The primary means to be used for requiring compliance with the standards shall be through best management practices required in waste discharge permits, rules, orders, and directives issued by the department for activities which generate storm water pollution. The consideration and control procedures in (b) and (c) of this subsection apply to the control of pollutants in storm water.

(4) **Allowance for compliance schedules.**

(a) Permits, orders, and directives of the department for existing discharges may include a schedule for achieving compliance with water quality criteria contained in this chapter. Such schedules of compliance shall be developed to ensure final compliance with all water quality-based effluent limits in the shortest practicable time. Decisions regarding whether to issue schedules of compliance will be made on a case-by-case basis by the department. Schedules of compliance may not be issued for new discharges. Schedules of compliance may be issued to allow for: (i) construction of necessary treatment capability; (ii) implementation of necessary best management practices; (iii) implementation of additional storm water best management practices for discharges determined not to meet water quality criteria following implementation of an initial set of best management practices; (iv) completion of necessary water quality studies; or (v) resolution of a pending water quality standards' issue through rule-making action.

(b) For the period of time during which compliance with water quality criteria is deferred, interim effluent limitations shall be formally established, based on the

best professional judgment of the department. Interim effluent limitations may be numeric or nonnumeric (e.g., construction of necessary facilities by a specified date as contained in an ecology order or permit).

(c) Prior to establishing a schedule of compliance, the department shall require the discharger to evaluate the possibility of achieving water quality criteria via noncontruction changes (e.g., facility operation, pollution prevention). Schedules of compliance may in no case exceed ten years, and shall generally not exceed the term of any permit.

[Statutory Authority: Chapter 90.48 RCW. 92-24-037 (Order 92-29), 173-201A-160, filed 11/25/92, effective 12/26/92.]

Legislature **Code Reviser** **Register**

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 10
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Seattle, WA 98101-3140

OFFICE OF
WATER AND
WATERSHEDS

DEC 19 2013

The Honorable Rudy Peone
Chairman
Spokane Tribe of Indians
P.O. Box 100
Wellpinit, Washington 99040

Re: EPA's Action on the Spokane Tribe of Indians 2010 Revision to Their Surface Water Quality Standards

Dear Chairman Peone:

The U.S. Environmental Protection Agency (EPA) has completed its Clean Water Act (CWA) review of the new and revised water quality standards that the Spokane Tribe submitted to the EPA on April 7, 2010. Under CWA Section 303, 33 U.S.C § 1313, tribes that are authorized for treatment in a manner similar to a state for the purpose of administering a water quality standards program must establish water quality standards and submit them to the EPA for approval or disapproval. Likewise, revisions to a tribe's water quality standard must also be submitted to the EPA for approval or disapproval. A summary of the EPA's actions is provided below and further described in the enclosed *Technical Support Document for Action on the Revised Surface Water Quality Standards of the Spokane Tribe of Indians Submitted April 2010* (hereafter referred to as the TSD).

Summary of the EPA's Action

I. Pursuant to the EPA's authority under CWA Section 303(c) and implementing regulations found at 40 CFR Part 131, the EPA is approving the following provisions:

- Section 2, Definitions
  - 7-day average of the daily maximum
  - Federal clean up law
  - Mixing zone
  - Nonpoint source
  - Trophic state
- Section 6, Narrative Provisions
  - Provision 5 – application of non-carcinogenic material
  - Minor editorial changes
- Section 6, Human Health Criteria (µg/L) in Table 1
  - 160 of 210 new or revised criteria are being approved (see Section V.D.1, page 23 for a list of criteria that are approved).
- Section 9, Temperature Criteria for Class AA waters

  This provision is being approved in part and disapproved in part. The EPA is approving the part that states: "Temperatures from June 1 to September 1 may be allowed to reach a

7-day average of the daily maximum (7-DADM) temperatures of 16.5 C.....The 7-DADM temperature shall not exceed 11°C between October 1st and March 31st."

- Section 11, Surface Water Classification
  - Specific classification of Ente' Creek as Class AA, and correction of spelling of Chamokane (Tshimikain) Creek.
- Section 13, Mixing Zone Provision
  - The EPA is approving this provision but notes that there is a typographical error in provision (2)(c). This provision should reference subsection (e) rather than subsection (f). This should be corrected when the Tribe does its next water quality standards revision (i.e., provision (2)(c) should state "overlapping mixing zones shall only be allowed if, in combination, the requirements of subsection (e) are satisfied; and").

II. Pursuant to the EPA's authority under CWA Section 303(c) and implementing regulations found at 40 CFR Part 131, the EPA is disapproving the following provisions:

- Section 6, Narrative Provisions
  - Provision 9, which states "Site-specific numerical criteria as described in the Tribal Cleanup Law must be developed in the event these assumptions are incorrect. If natural background conditions exceed the risk criteria defined in this section, then the natural background conditions are the numerical standard."
- Section 6, Human Health Criteria (µg/L) in Table 1
  - Removal of Asbestos criterion from Table 1 (see Section V.D.2 of TSD, page 25).
  - Criteria for Dichlorodiflouromethane (Section V.D.3 of TSD, page 26), Mercury (Section V.D.4 of TSD, page 28), and 45 other criteria (Section V.D.5. Table 4 in the TSD for a list of the pollutants, page 29).
- Section 6, Aquatic Life Criteria in Table 1
  - Revisions to acute and chronic aquatic life ammonia criteria.
  - Revisions to acute and chronic aquatic life pentachlorophenol criteria.
    - Removal of chronic aquatic life criterion for iron.
- Section 9, Temperature Provisions for Class AA and Class A waters
  - Provision (1)(c)(4) for Class AA waters. This provision is being approved in part and disapproved in part. The EPA is disapproving the part that states: "Temperature shall not exceed the 7-DADM Table 5 value from September 1st through September 30th as well as from April 1st through May 31st." The EPA is also disapproving the associated temperature criteria for Class AA waters contained in Table 5.
  - Provision (2)(c)(iv), temperature revisions for Class A waters. The EPA is disapproving the entire provision, which states: "temperatures (sic) from June 1 to August 31 may be allowed to reach a 7-day average (7-DADM) of the daily maximum temperature of 18.5° C. Temperature shall not exceed the 7-DADM Table 5 value from September 1st through September 30th as well as from April 1st through May 31st. The 7-DADM temperature shall not exceed 11°C between October 1st and March 31st." The EPA is also disapproving the associated temperature criteria for Class A waters contained in Table 5.

III. The EPA is not taking action on the following provisions because they are not considered water quality standards under Section 303(c) of the CWA:

- Section 1, Introduction
  - New language in provision 4 and 6.
- Section 2, Definitions
  - 1-day maximum temperature
  - Background
  - Cumulative Risk
- Section 6, Narrative Provisions
  - Provisions 6 and 7 fish consumption rate and drinking water intake rate. The language in provision 6 and 7 provide two of the input values used by the Tribe to develop the human health criteria. The EPA incorporated this information into its analysis of the individual human health criteria. Because these two provisions do not operate as independent water quality standards, in isolation from the human health criteria, the EPA is taking no action to approve or disapprove them.
  - The EPA did not act on the following language in provision 9:
    "Table 1 is developed using the following assumptions:
    a. the receptor (e.g. human) receives a dose from a single contamination (e.g. cadmium) from a single medium (e.g. surface water) via direct ingestion of water or fish and waters; and
    b. the dose from natural background condition is negligible."

Additional information and a detailed discussion of the rationale supporting all of the EPA's actions is included in the enclosed TSD.

Background on the EPA's Evaluation of the Revised Human Health Criteria
The most significant change made in the Spokane Tribe's 2010 Water Quality Standards submittal was the Tribe's revisions to their human health toxics criteria, including the use of a new fish consumption rate of 865 grams per day and drinking water intake rate of 4 liters per day. As a result of these revisions, the Spokane Tribe's human health toxics criteria are generally more stringent than the default values recommended by the EPA in national guidance, which are provided to assist states and tribes who may not have the data or resources to develop their own criteria values. Due to the current public attention and interest in human health water quality criteria and how they are derived, a brief summary of the EPA's decision rationale for the human health criteria revisions is provided below. As previously noted, a more detailed discussion is provided in the enclosed TSD.

The EPA's regulations at 40 CFR § 131.11(a) provide that new or revised criteria "must be based on sound scientific rationale and must contain sufficient parameters or constituents to protect designated uses." If these requirements are met, states and tribes are able to develop criteria that may be more (or less) stringent than those recommended by the EPA. The EPA evaluated the Spokane Tribe's revised human health criteria as follows:

- First, the EPA acknowledged the Tribe's decision to ensure water quality sufficient to support traditional subsistence practices, which is fundamentally a question of tribal policy and within

their authority under the CWA. The CWA does not require that decision to be justified by reference to the number of persons who currently rely on tribal waters for such purposes.

- Second, the EPA evaluated the scientific defensibility of the assumptions and methodology the Tribe used in deriving criteria to protect its water quality goals, including the derivation of fish consumption and drinking water rates characteristic of the Spokane Tribe's subsistence traditions.
- Third, the EPA evaluated whether the Tribe's criteria are sufficient to protect not only 304(a) fishable/swimmable goals but also the goal of protecting fish consumption and drinking water rates characteristic of the traditional Spokane subsistence lifestyle.

The EPA is approving the majority of the Tribe's revised human health criteria because the methodology used by the Tribe to develop the fish consumption rate, and other variables used in developing the criteria, are scientifically sound and sufficient to protect the designated uses, which are designed to protect fish consumption and drinking water rates characteristic of the traditional Spokane subsistence lifestyle. The EPA is disapproving some of the revised human health criteria because they were not scientifically defensible and were not protective of the Tribe's designated uses.

Remedy to Address the EPA's Disapproval Actions

Under CWA Section 303(c)(3) and the EPA's regulations at 40 CFR Sections 131.21 and 131.22, if the EPA disapproves a state or tribe's new or revised water quality standards, it must "specify the changes" necessary to meet the applicable requirements of the CWA and the EPA's regulations. As previously noted, a comprehensive summary of the EPA's actions and the specific changes necessary for each disapproval are included in the TSD.

The EPA has appreciated our work together throughout this process and we remain committed to providing assistance to the Tribe in its development of WQS that meet the requirements of the CWA and its implementing regulations. We also look forward to engaging with you and others in the Spokane River Basin to ensure thoughtful consideration of your WQS in water quality protection and improvement efforts. If you have any questions concerning this letter, please contact me at (206) 553-1855 or you may contact Angela Chung, Water Quality Standards Unit Manager, at (206) 553-6511.

Sincerely,

Daniel D. Opalski, Director
Office of Water and Watersheds

Enclosures

cc: Brian Crossley, Spokane Tribe of Indians
BJ Keiffer, Spokane Tribe of Indians

U.S. ENVIRONMENTAL PROTECTION AGENCY – REGION 10

Technical Support Document

for Action on the Revised Surface Water Quality Standards of the Spokane Tribe of Indians Submitted April 2010

December 11, 2013

TABLE OF CONTENTS

Contents

I. INTRODUCTION

This document provides the basis for EPA's decisions under the federal water quality standards regulations at 40 CFR § 131.11 and § 303(c) of the Clean Water Act (CWA) to approve or disapprove the new or revised water quality standards that the Spokane Tribe of Indians ("Tribe") submitted to EPA on April 7, 2010.

A. Background

In 2006, the Tribe began the process of revising the *Spokane Tribe of Indians Surface Water Quality Standards* (WQS). The Spokane Tribal Business Council (TBC), the governing body of the Tribe, adopted the draft revised WQS on July 29, 2008.

The Tribe provided a 45-day formal public comment period on the draft revisions, and held a public hearing on October 1, 2008. Additionally, an e-mail was sent to local governments and Spokane River stakeholders notifying interested parties of proposed changes, and notification was placed on the Washington Department of Ecology listserve.

Final revisions to the WQS were adopted by the TBC on February 25, 2010, by Resolution 2010-173. The Tribe's submittal included a letter dated March 15, 2010, from Ted C. Knight, Attorney-at-Law, certifying that the revisions were adopted in accordance with all applicable laws. In accordance with § 303(c) of the CWA, the Tribe submitted these revisions to EPA for review and action in a letter dated April 7, 2010.

The revisions addressed in today's decision can be divided into the general categories described below.

- Revisions to the Introductory language to the water quality standards
- New definitions
- Revised human health criteria based on consuming 865 g of fish per day and 4 liters of water per day
- Revised aquatic life criteria
- Revised temperature criteria for waters designated as Class AA and Class A
- New mixing zone provisions
- Minor editorial and formatting changes

B. Clean Water Act Requirements for Water Quality Standards

Under § 303(c) of the CWA and federal implementing regulations at 40 CFR § 131.4, states and authorized tribes[1] have the primary responsibility for reviewing, establishing, and revising WQS, which consist of the designated uses of a waterbody or waterbody segment, the water quality criteria necessary to protect those designated uses, and an antidegradation policy. This statutory framework allows states to work with local communities to adopt appropriate designated uses (as required in 40 CFR § 13l.10 (a)) and to adopt criteria to protect those designated uses (as required in 40 CFR § 131.11 (a)).

[1] The term "authorized tribe" means a tribe eligible under CWA § 518(e) and 40 CFR § 131.8 for treatment in a manner similar to a state for the purpose of administering a water quality standards program.

States are required to review applicable WQS, and as appropriate, modify and adopt these standards (40 CFR § 131.20). Each state must follow its own legal procedures for adopting such standards (40 CFR § 131.5) and submit certification by the state's attorney general or other appropriate legal authority within the state that the WQS were duly adopted pursuant to state law (40 CFR § 131.6(e)).

Section 303(c)(2)(B) of the CWA requires states to adopt water quality criteria for toxic pollutants listed pursuant to § 307(a)(1) for which EPA has published criteria under § 304(a) where the discharge or presence of these toxics could reasonably be expected to interfere with the designated uses adopted by the state. In adopting such criteria, states must establish numeric values based on one of the following:

(1) 304(a) guidance;
(2) 304(a) guidance modified to reflect site-specific conditions; or,
(3) Other scientifically defensible methods (40 CFR § 131.11 (b)(1)).

In addition, states can establish narrative criteria where numeric criteria cannot be determined or to supplement numeric criteria (see 40 CFR § 131.11(b)(2)).

Section 303(c) of the CWA also requires states to submit new or revised WQS to EPA for review. EPA is required to review these changes to ensure revisions to water quality standards are consistent with the CWA. EPA determines whether a provision is a new or revised WQS after considering the following four questions:[2]

(1) Is it a legally binding provision adopted or established pursuant to state or tribal law?
(2) Does the provision address designated uses, water quality criteria (narrative or numeric) to protect designated uses, and/or antidegradation requirements for waters of the United States?
(3) Does the provision express or establish the desired condition (e.g. uses, criteria) or instream level of protection (e.g. antidegradation requirements) for waters of the United States immediately or mandate how it will be expressed or established for such waters in the future?
(4) Does the provision establish a new WQS or revise an existing WQS?

Furthermore, the federal water quality standards regulations at 40 CFR § 131.21 state, in part, that when EPA disapproves a state's water quality standards, EPA shall specify the changes that are needed to ensure compliance with the requirements of § 303(c) of the CWA and federal water quality standards regulations.

II. INTRODUCTORY LANGUAGE (Section 1, Provisions 4 and 6)

A. Provisions that EPA Is Not Taking An Action On

The following presents the new and revised introductory language to the WQS contained in Section 1, provisions 4 and 6. All underlined text indicates language that is new and strikeout text indicates the language that was removed by the 2010 water quality standards adoption.

[2] See EPA's *What Is A New or Revised Water Quality Standard Under CWA 303(c)(3)? Frequently Asked Questions*, October 2012 at http://water.epa.gov/scitech/swguidance/standards/cwa303faq.cfm

…(4) These standards are designed to establish the uses for which the surface waters of the Spokane Tribe shall be protected, to prescribe narrative and numeric water quality criterion to sustain the designated uses, to protect existing water quality, and to prevent water quality degradation.

As part of this chapter:

(a) All surface waters are protected by narrative criteria, designates uses, and an antidegradation policy.

(b)Based on the use designations, numeric and narrative criteria are assigned to a water body to protect the existing and designated uses.

(c) Where multiple criteria for the same water quality parameter are assigned to a water body to protect different uses, the most stringent criteria for each parameter is to be applied.

(d) Where multiple contaminants of concern have been identified or where multiple media has been contaminated, or where more than one exposure pathway has been identified, water quality standards shall be determined using the cumulative risk assessment approach and definitions described in the Tribal Cleanup Law.

(5) The Water use and quality criteria set forth herein are established in general conformance with water uses of the surface waters of the Spokane Indian Reservation and in consideration of the natural water quality potential and limitations of the same.

(6) The Surface Water Quality Standards were first adopted by the Spokane Business Council on December 17, 1999 by Resolution 2000-105. As a result of public comments received after hearings were held on February 10, 2000, the standards were revised on June 19, 2000, by Resolution 2000-105. To address further comments these standards were again revised on February 13, 2001, by Resolution 2001-144. Finally, the standards were revised on March 7, 2003, by Resolution 2003-244 to address a technical correction identified by staff. These revised standards supersede and replace all previous standards. These revised standards supersede and replace the ~~June 19, 2000~~ all previous standards. These standards shall become effective on the date of adoption, and shall be applicable and in force, to the full extent of the law, until repealed or replaced by the Spokane Business Council.

EPA Action

Section I of the Tribe's water quality standards provides an introduction to the water quality standards language[3]. The introduction discusses the Executive Order confirming that the Spokane Reservation is reserved for the Spokane Tribe of Indians, describes the Tribe's authority to adopt standards, and sets forth the purposes of the standards. EPA acknowledges the new and revised language contained in provisions 4 and 6 of the introductory language. However, water quality standards are provisions of Tribal or Federal law that consist of designated uses for waters of the United States, water quality criteria necessary to protect those designated uses, and an antidegradation policy (40 CFR § 131.3(i)). Provision 4 is a general statement describing what the water quality standards are intended to achieve. The new language added to provision 4 is simply outlining what is contained in Sections 2 through 14 of the water quality standards (e.g., the water

[3] On April 22, 2003 EPA approved the Tribe's Original water quality standards. In that decision EPA did not act on any of the provisions contained in Section I because they were not considered water quality standards they are simply introducing concepts that are in the body of the water quality standards.

quality standards provisions outline in 4(c) and (d) are contained in Section 6, provision 9). Provision 6 merely discusses the history of various rulemakings. The provisions do not establish designated uses or criteria to protect the uses and as such are not a water quality standard under § 303(c) of the CWA. Therefore, EPA is not required to take an action on these provisions under the CWA.

III. DEFINITIONS (SECTION 2)

A. Definitions that EPA Is Not Taking An Action On

All new text is underlined and indicates the language that was added in the 2010 water quality standards adoption. EPA is not taking an action on the following definitions because they are not water quality standards:

1. ***"1-day maximum temperature" or "1-dm"****is the highest water temperature reached on any given day. This measure can be obtained using calibrated maximum/minimum thermometers or continuous monitoring probe having sampling intervals of thirty minutes or less.*

2. *"**Background**" means the natural three dimensional distribution of physico-chemical conditions associated with the volume of media in which the release occurred, prior to the release. In many instances, location immediately outside of the nature and extent of contamination can be used by the Department to determine background. In instances in which no such locations are available, the Department shall identify an "appropriate reference site or region."*

3. *"**Cumulative Risk**" means risk caused from post release doses from multiple pathways, multiple media (primary and secondary sources), and/or multiple hazardous substances. This definition is consistent with Tribal cleanup law.*

These three terms are not referenced in any provision within the Tribe's water quality standards. For example, the 1-day maximum temperature (1-dm) is a metric for temperature, however, the temperature criteria in the Tribe's water quality standards are expressed as a 7-day average of the daily maximum temperatures not a 1-day maximum. Because these terms are not used in any water quality criteria or provision, they do not establish a legally binding requirement under tribal law nor do they describe a desired ambient condition of a water body to support a particular designated use. Therefore, the terms and the associated definitions are not water quality standards subject to EPA review and approval under 303(c) of the CWA and EPA is taking no action to approve or disapprove these new terms and definitions.

EPA recommends the Tribe delete the terms and definitions from their water quality standards since they are not relevant.

.

B. Definitions that EPA is Taking Action On

The following presents the new definitions contained in Section 2 of the WQS. All new text is underlined and indicates the language that was added in the 2010 water quality standards adoption.

1. ***"7-day average of the daily maximum temperatures or 7-DADM"*** *is the arithmetic average of seven consecutive measures of daily maximum temperatures. The 7-DADM for any individual day is calculated by averaging that day's daily maximum temperature with the daily maximum temperatures of the three days prior and the three days after that date.*

EPA Action

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the definition for "7-day average of the daily maximum temperatures or 7-DADM" because it is scientifically defensible, protective of the use, and consistent with § 303(c) of the CWA and its implementing regulations.

The 7-DADM metric is the metric used for temperature criteria in the Tribe's water quality standards. The 7-DADM metric is recommended for temperature standards by the USEPA *Region 10 Guidance for Pacific Northwest State and Tribal Temperature Water Quality Standards* (EPA910-B-03-002, April 2003, hereafter referred to as the Temperature Guidance). The Temperature Guidance and the six Technical Issue Papers that serve as the scientific basis for the recommendations in this document may be found at: www.epa.gov/r10earth/temperature.htm.

The 7-DADM metric adequately protects aquatic life against acute[4] effects because it incorporates daily maximum temperatures. This metric can also be protective of chronic[5] effects to aquatic life because it describes the thermal exposure over 7 days. The Temperature Guidance considered both acute and chronic effects to fish when developing its recommended temperature criteria.

2. *"Federal clean up law" means the Comprehensive Environmental Response, Compensation and Liability Act, 42, U.S. Sec.9601, et seq."*

EPA Action

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the definition for "Federal clean up law" because it is needed for the proper implementation of the Tribe's mixing zone policy, which defines the limited circumstances under which a mixing zone may be allowed.

3. *"Mixing zone" means that portion of a water body affected by the discharge of effluents in accordance with Section 13(2) of this chapter where mixing results in the dilution of the effluent with the receiving water.*

EPA Action

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the definition for "mixing zone" because it provides information needed for the application and implementation of WQS. In addition, it is consistent with the definition incorporated into EPA guidance (Technical Support Document for Water Quality-based Toxics Control (EPA, March 1991)).

[4] Acute – a stimulus severe enough to rapidly induce an effect such as lethality.
[5] Chronic - a stimulus that lingers over a relatively long period of time. It is measured as reduced growth, reduced reproduction, lethality, etc.

4. *"Nonpoint source" means pollution that enters any waters of the reservation from any dispersed land based or water-based activities, including but not limited to atmospheric deposition, surface water runoff from agricultural lands, urban area, or forest lands, subsurface or underground sources, or discharges from boats or marine vessels not otherwise regulated under the National Pollutant Discharge Elimination System.*

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the definition for "nonpoint source" because it is generally consistent with the EPA guidance (*NPDES Permit Writer's Manual*, EPA-833-K-10-001, September 2010).

5. *"Tribal clean up law" means the Hazardous Substances Control Act, Chapter 34, Law and Order Code of the Spokane Tribe of Indians.*

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the definition for "Tribal clean up law" because the term is needed for the implementation of the Tribe's mixing zone policy, which defines the limited circumstances under which a mixing zone may be allowed.

6. *"Trophic state" means a classification of the productivity of a lake ecosystem. Lake productivity depends on the amount of biologically available nutrients in water and sediment and may be based on total phosphorus (TP). Secchi depth and chlorophyll-a measurements may be used to improve the trophic state classification of a lake. Trophic states used in this rule include oligotrophic, lower mesotrophic, upper mesotrophic, and eutrophic.*

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the definition for "trophic state" because it explains the term as it is used in the water quality standards.

IV. NARRATIVE PROVISIONS (SECTION 6, Provisions 5 through 9)

A. EPA Action on Narrative Provisions

The following presents the new and revised language to the WQS contained in Section 6, provisions 5 through 9. All underlined text indicates language that is new and strikeout text indicates the language that was removed by the 2010 water quality standards adoption.

~~*(5) The aquatic organism consumption rate utilized in determining the human health criteria shall be 86.3 g/day. This figures does not reflect the actual consumption rate typical of the Spokane Tribe of Indians, but has been used for the limited purpose of establishing these Surface*~~

~~*Water Quality Standards based on current EPA guidance (63 F.R. 43756). This rate may be modified to reflect consumption rate analysis specific to the Spokane Tribe.*~~

(5) Human-health risk-based criteria for non-carcinogenic material shall be applied such that the hazard index, as defined in the Tribal Cleanup Law for a given mixture, does not exceed 1.0.

~~*(6) The guidelines set forth in 40 CFR Part 136 shall be used as guidance for analytical methodologies.*~~

(6) The aquatic organism consumption rate utilized in determining the human health criteria shall be 865 g/day.

~~*(7) The criteria in Table 1 shall be applied to all surface waters of the tribe for the protection of aquatic life and human health. The concentration for each compound listed in Table 1 is a criterion for aquatic life or human health protection. Selecting values for regulatory purposes will depend on the most sensitive beneficial use to be protected and the level of protection necessary for aquatic life and human health as specified within Table 1. Application for a reduction in the list of compounds or elements must be based on proof that one or more of the proposed compounds are not of concern. Authorization of such a reduction is at the discretion of the Department. All concentrations, except asbestos, are micrograms per liter (µg/L).*~~

(7) The surface water consumption rate utilized in determining the human health criteria shall be 4 L/day.

(8) The guidelines set forth in 40 CFR Part 136 shall be used as guidance for analytical methodologies.

(9) The criteria in Table 1 shall be applied to all surface waters of the tribe for the protection of aquatic life and human health. The concentration for each compound listed in Table 1 is a criterion for aquatic life or human health protection. Table 1 is developed using the following assumptions:

a. the receptor (e.g. human) receives a dose from a single contaminant (e.g. cadmium) from a single medium (e.g. surface water) via direct ingestion of water or fish and water; and

b. the dose from natural background conditions is negligible,

Site-specific numerical criteria as described in the Tribal Cleanup Law must be developed in the event these assumptions are incorrect. If natural background conditions exceed the risk criteria defined in this section, then the natural background conditions are the numerical standard.

Selecting values for regulatory purposes will depend on the most sensitive beneficial use to be protected and the level of protection necessary for aquatic life and human health as specified within Table 1. Application for a reduction in the list of compounds or elements must be based on proof that one or more of the proposed compounds are not of concern. Authorization of such a reduction is at the discretion of the Department. All concentrations, except asbestos, are micrograms per liter (µg/L).

EPA Action

Section 6, Provision (5)

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the new Provision (5), which states: *(5) Human–health risk-based criteria for non-carcinogenic material shall be applied such that the hazard index, as defined in the Tribal Cleanup Law for a given mixture, does not exceed 1.0.*

The hazard index (HI) is the sum of hazard quotients (HQs) for substances that affect the same target organ or organ system. Because different pollutants can cause similar adverse health effects, it may be appropriate to combine HQs associated with different substances. A HQ is the ratio of potential exposure to the substance and the level at which no adverse effects are expected. If the HQ is calculated to be less than 1 then no adverse effects are expected as a result of exposure. Similarly, aggregate exposures below a HI of 1.0 would likely not result in adverse non-cancer health effects.

EPA is approving this provision because it is a reasonable methodology to ensure that mixtures of chemicals do not adversely affect the human health uses adopted by the Tribe.

Section 6, Provisions (6) and (7)

Provision (6) provides the fish consumption rate used to develop the human health criteria and provision (7) provides the surface water consumption rate used to develop the human health criteria. EPA is not taking action on provisions (6) and (7) because the language does not establish a legally binding requirement under tribal law and it does not describe a desired ambient condition of a waterbody to support a particular designated use. Therefore it is not considered a WQS subject to EPA review and approval under 303(c) of the CWA.

EPA has addressed the new and revised human health criteria in Section 6, Table 1 of the tribal water quality standards in this technical support document. The language in provisions (6) and (7) explains two of the inputs used when the Tribe derived their human health criteria values (see Section 6, in Table 1 of the water quality standards for the human health criteria). EPA incorporated the explanatory information provided in these two provisions into its analysis of the individual human health criteria values in Section 6, Table 1. However, because these two provisions do not operate as independent water quality standards in isolation from the human health criteria values contained in Table 1, EPA is taking no action to approve or disapprove provisions (6) and (7).

It should be noted that the Tribe's 2003 water quality standards contained a provision which stated that the fish consumption rate of 86.3 g/d (in the 2003 WQS the fish consumption rate was in Section 6, provision 5, when the Tribe revised its water quality standards in 2010 some provisions were re-numbered, in the 2010 water quality standards the fish consumption rate is contained in provision 6) and in April 2003 EPA approved that provision. EPA hereby rescinds its 2003 approval of the fish consumption rate based on the above analysis.

Provision 9

EPA is not taking on action on part of Provision 9, and is disapproving part of Provision 9.

- EPA not taking action on the following new language added to provision 9 because it is not a water quality standard:

  Table 1 is developed using the following assumptions:

  a. the receptor (e.g. human)receives a dose from a single contamination (e.g. cadmium) from a single medium (e.g. surface water) via direct ingestion of water or fish and water; and

  b. the dose from natural background conditions is negligible.

EPA is not taking action on the above language because it does not establish a legally binding requirement under tribal law and it does not describe a desired ambient condition of a waterbody to support a particular designated use, therefore, it is not considered a WQS subject to EPA review and approval under 303(c) of the CWA. This language simply explains two of the assumptions used in developing criteria. EPA considered these assumptions in its analysis of the individual criteria values in Section 6, Table 1. But because these two assumptions do not operate as independent water quality standards, in isolation from the criteria values in Section 6, Table 1 of the tribal water quality standards (which EPA acted on individually), EPA is taking no action to approve or disapprove this new language in provision 9.

- In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the following new language in Provision (9):

  Site-specific numerical criteria as described in the Tribal Cleanup Law must be developed in the event these assumptions are incorrect. If natural background conditions exceed the risk criteria defined in this section, then the natural background conditions are the numerical standard.

EPA is disapproving this language because it requires that the criteria be revised should the assumptions in Provision 9.a and 9.b be incorrect. While it may be appropriate to develop site-specific criteria, this provision does not require that the revised criteria be subject to a public involvement process, be adopted into the Spokane Tribal water quality standards, or be submitted to EPA for review and approval as required in 40 CFR Part 131.

EPA's water quality standards regulations do not provide specific requirements for establishing criteria based on natural background conditions. However, any water quality criteria adopted by states or tribes must be established based on a sound scientific rationale and assure protection of designated uses (see 40 CFR § 131.11(a)(1)). This would include establishing criteria based on natural background conditions.

EPA's November 1997 policy titled *Establishing Site Specific Aquatic Life Criteria Equal to Natural Background* recognized that there may be naturally occurring concentrations of pollutants which may exceed the national criteria published under § 304(a) of the CWA. This policy articulates that States and Tribes may establish site specific numeric aquatic life water quality criteria by setting the criteria value equal to the natural background of a waterbody.

Natural background is defined as the background water quality concentration due only to non-anthropogenic sources. The policy explains that "For aquatic life uses, where the natural background concentration for a specific parameter is documented, by definition that concentration is sufficient to support the level of aquatic life expected to occur naturally at the site absent any interference by humans."

In setting criteria equal to natural background, the policy recommends that "…the State or Tribe should, at a minimum, include in their water quality standards:

> (1) a definition of natural background consistent with the above;
> (2) a provision that site specific criteria may be set equal to natural background;
> (3) a procedure for determining natural background, or alternatively, a reference in their water quality standards to another document describing the binding procedure that will be used."

Furthermore, it explains that where the natural background concentration exceeds the state adopted human health criterion, at a minimum, the State or Tribe should re-evaluate the human health use designation. The policy states that "it does not apply to human health uses."

The Tribe has not developed guidance describing the binding procedure that would be used to determine the natural background. Additionally, the regulatory language in provision (9) allows the "natural background condition" to become the criterion for human health criteria as well as aquatic life uses.

Impacts to humans due to exposure to waterborne toxicants occur through three primary routes: contact recreation; drinking water; and ingestion of contaminated fish and shellfish tissues. The human health protection criteria are based on data regarding human absorption, distribution, metabolism, and excretion of toxic pollutants. Human health effects from toxicants are divided into categories based on the human biological endpoints observed as well as data on human acute, sub-acute, and chronic toxicity, synergistic and antagonistic effects, and specific information on human mutagenicity, teratogenicity, and carcinogenicity. In addition, the human health methodology used to develop human health criteria includes the contribution of other sources, such as dietary intake other than fish and air inhalation, in the assessment of total exposure to a pollutant.

The level of a naturally occurring pollutant does not necessarily protect human health or designated uses which may include people drinking directly from streams, and/or eating fish and shellfish. In cases where the natural condition exceeds the numeric criteria, an evaluation of whether the natural level would protect human health uses is needed. An evaluation of whether the human health uses are supported by the natural condition criterion would include an assessment of potential and known human exposure pathways and any risks to adverse human health effects of the pollutant at the natural condition concentrations. Because human exposure and health effects assessments are not part of this provision and no guidance for implementing its "natural background condition" provision has been developed, there is no evaluation as to whether or not the naturally occurring level protects human health uses. Consistent with the CWA and the federal regulations, the Tribe must assure that the water quality criteria provide protection to the designated uses.

EPA has determined that the new language in provision 9 (i.e., *Site-specific numerical criteria as described in the Tribal Cleanup Law must be developed in the event these assumptions are incorrect. If natural background conditions exceed the risk criteria defined in this section, then the natural background conditions are the numerical standard.)* is inconsistent with the CWA and the federal water quality standards regulations at 40 CFR § 131.l1(a), because this provision allows the Tribe to establish criteria based on natural conditions that do not assure protection of the designated human health uses in tribal waters. The level of a naturally occurring pollutant does not necessarily protect designated human health uses. Natural levels of a pollutant are assumed to protect aquatic life species which naturally occur in these waters. However, waterbodies are not the natural habitat for humans and therefore, the same assumptions of protectiveness cannot be made with regard to human health uses (e.g., people drinking directly from streams, eating fish or shellfish from tribal waters, and recreating in tribal waters). Therefore, the tribe has not demonstrated how its approach would protect designated human health uses. Additionally, as mentioned previously, the Tribe has not provided EPA with a binding procedure for determining natural background conditions as envisioned by EPA's November 1997 policy.

Remedy to Address EPA's Disapproval

To address this disapproval, the Tribe could delete the provision as the Tribe's approved numeric criteria are protective of designated uses. Additionally, the Tribe may use the natural condition provision in Section 3, Provision 2 of its water quality standards which states that the "…the Department may determine that the natural conditions shall constitute the water quality criteria." In a December 26, 2000 letter from Rudy Peone it was clarified that any natural condition criterion will be developed as a site specific criterion that would be submitted to EPA for review and approval.

Alternatively, the Tribe could revise the water quality standard to clarify that it applies only to aquatic life criteria and adopt into its WQS (directly or by reference) a binding methodology[6] that provides a transparent, predictable, repeatable, and scientifically defensible procedure for the protection of designated aquatic life uses. This approach, known as a "performance-based" approach, relies on the adoption of a systematic process (i.e., a criterion derivation methodology) rather than a specific outcome (i.e., concentration limit for a pollutant) consistent with 40 CFR § 131.11 and 131.13. EPA would need to review any such binding methodology that the Tribe develops as part of a performance-based approach. The performance-based approach could be used to derive site-specific adjustments to numeric criteria or to translate a narrative criterion into quantifiable measures. When such a performance-based approach is sufficiently detailed and has suitable safeguards to ensure predictable, repeatable outcomes, the EPA approval of such an approach also serves as approval of the outcomes as well. Note, however, that one approach is likely not suited to derive all pollutant targets and metrics given the breadth of pollutants over which the natural condition criterion applies. Individual methodologies for each pollutant or subsets of pollutants with similar sources and cycling would likely be necessary in order to ascertain the scientific defensibility of the methodology and the level of protection afforded to designated uses as a result of using the methodology.

[6] EPA 2000. *EPA Review and Approval of State and Tribal Water Quality Standards.* Federal Register: April 27, 2000 (Volume 65, Number 82); Rules and Regulations; Page 24641-24653. Procedures to identify opportunities by which their adoption of criteria, as well as EPA's approval, can be streamlined.

B. EPA Action On Editorial Changes Section 6, Provisions 5 through 9

Minor Editorial Changes made to Provisions 5 through 9

In addition to the new language added in Provisions (5) through (9) the provisions were re-numbered. EPA acknowledges the re-numbering of provisions (5) through (9) as minor editorial changes and approves them as non-substantive changes.

V. Human Health Criteria in Section 6, Table 1

Table 1, below, presents the new and revised human health criteria for "water and organisms" and for "organisms only" as well as the revised aquatic life criteria. All new or revised criteria included in the 2010 water quality standards adoption are underlined and are expressed as *µg/L*.

Compound	*Carcinogen?*	*Acute (a) Criteria*	*Chronic (b) Criteria*	*Water & Organisms*	*Organisms Only*
Acenaphthene	*n*			*1.97E+01*	*2.01E+01*
Acrolein	*n*			*5.75E+00*	*5.87E+00*
Acrylonitrile	*y*			*4.33E-03*	*5.00E-03*
Aldrin (e)	*y*	*3.0E+00*	*1.9E-03*	*1.02E-06*	*1.02E-06*
Aluminum (pH 6.5 - 9.0)	*n*	*7.5E+02*	*8.7E+01*	-----	-----
Ammonia, un-ionized (f, g)	*n*	*2.4E+04*	*5.9E+03*	-----	-----
Anthracene	*n*			*7.01E+02*	*8.09E+02*
Antimony	*n*			*5.76E+00*	*3.24E+01*
Arsenic (h)	*y*	*3.4E+02*	*1.5E+02*	*9.51E-04*	*1.05E-03*
Asbestos	*y*			*see footnote 1*	-----
Barium	*n*			*1.00E+03*	-----
Benz(a)anthracene	*y*			*3.2E-04*	*3.7E-04*
Benzene	*y*			*2.84E-01*	*5.37E-01*
Benzidine	*y*			*3.82E-06*	*4.02E-06*
Benzo(a)pyrene	*y*			*3.2E-04*	*3.7E-04*
3,4-Benzo(b)fluoranthene	*y*			*3.2E-04*	*3.7E-04*
Benzo(k)fluoranthene	*y*			*3.2E-04*	*3.7E-04*
alpha BHC	*y*			*9.54E-05*	*9.88E-05*
beta BHC	*y*			*3.34E-04*	*3.46E-04*
gamma BHC (e)	*y*	*9.5E-01*	*8.E-02*	*4.53E-04*	*4.69E-04*
Bis(2-chloroethyl) Ether	*y*			*6.38E-03*	*1.07E-02*
Bis(2-chloroisopropyl) Ether	*n*			*4.56E+02*	*1.31E+03*
Bis(2-chloromethyl)ether	*y*			*7.00E-05*	*5.84E-04*
Bis(2-ethylhexyl)phthalate	*y*			*4.29E-02*	*4.45E-02*
Bromoform	*y*			*1.22E+00*	*2.73E+00*
Butylbenzyl phthalate	*n*			*3.87E+01*	*3.91E+01*
Cadmium (j)	*n*	*3.7E+00*	*1.0E+00*	*8.75E+00*	-----
Carbon tetrachloride	*y*			*2.66E-02*	*3.32E-02*
Chlordane (e)	*y*	*2.4E+00*	*4.3E-03*	*4.41E-06*	*4.41E-06*

Compound	Carcinogen?	Acute (a) Criteria	Chronic (b) Criteria	Water & Organisms	Organisms Only
Chloride		8.6E+05	2.3E+05	-----	-----
Chlorine	n	1.9E+01	1.1E+01	1.75E+03	-----
Chlorobenzene	n			1.08E+02	1.57E+02
Chlorodibromomethane	y			1.15E-01	2.57E-01
Chloroform	y			1.58E+00	3.54E+00
2-Chloronaphthalene	n			3.13E+01	3.20E+01
2-Chlorophenol	n			2.92E+00	3.02E+00
Chlorpyrifos	n	8.3E-02	4.1E-02	5.25E+01	-----
Chromium (Hex)	n	1.5E+01	1.0E+01	5.25E+01	-----
Chromium (Tri)	n	5.5E+02	7.4E+01	2.63E+04	-----
Chrysene	y			3.20E-04	3.70E-04
Copper	n	1.3E+01	9.0E+00	1.21E+01	1.21E+01
Cyanide	n	2.2E+01	5.2E+00	2.88E+02	1.62E+03
4,4'-DDD	y			6.29E-06	6.29E-06
4,4'-DDE	y			4.44E-06	4.44E-06
4,4'-DDT	y	1.1E+00	1.E-03	4.44E-06	4.44E-06
Demeton	n		1.E-01	-----	-----
Dibenz(a,h)anthracene	y			3.20E-04	3.70E-04
Dibutyl phthalate	n			8.64E+01	9.09E+01
1,2-(o)Dichlorobenzene	n			1.21E+02	1.31E+02
1,3-(m)Dichlorobenzene	n			1.80E+01	1.95E+01
1,4-(p)Dichlorobenzene	n			1.80E+01	1.95E+01
3,3-Dichlorobenzidine	y			5.68E-04	5.76E-04
Dichlorobromomethane	y			1.56E-01	3.48E-01
Dichlorodifluoromethane	n			1.93E+03	4.32E+03
1,2-Dichloroethane	y			1.53E-01	7.41E-01
1,2-trans-Dichloroethylene	n			2.61E+02	1.02E+03
1,1-Dichloroethylene	y			1.32E-02	2.41E-02
2,4-Dichlorophenol	n			5.36E+00	5.96E+00
1,2-Dichloropropane	n			1.40E-01	2.97E-01
1,3-Dichloropropylene	n			3.72E+00	1.27E+01
Dieldrin	y	2.4E-01	1.9E-03	1.08E-06	1.08E-06
Diethyl phthalate	n			8.34E+02	8.87E+02
2,4-Dimethylphenol	n			1.64E+01	1.73E+01
Dimethyl phthalate	n			1.99E+04	2.25E+04
2,4-Dinitrophenol	n			2.64E+01	1.08E+02
2,4-Dinitotoluene	y			3.06E-02	6.78E-02
2,3,7,8-TCDD (Dioxin)	y			1.04E-10	1.04E-10
1,2-Diphenylhydrazine	y			3.43E-03	4.06E-03
alpha Endosulfan	n	2.2E-01	5.6E-02	1.77E+00	1.80E+00
beta Endosulfan	n	2.2E-01	5.6E-02	1.77E+00	1.80E+00
Endosulfan sulfate	n			1.77E+00	1.80E+00
Endrin	n	8.6E-02	2.3E-03	6.11E-03	6.12E-03
Endrin aldehyde	n			6.11E-03	6.12E-03
Ethylbenzene	n			1.92E+02	2.16E+02
Fluoranthene	n			2.80E+00	2.81E+00

Compound	Carcinogen?	Acute (a) Criteria	Chronic (b) Criteria	Water & Organisms	Organisms Only
Fluorene	n			9.35E+01	1.08E+02
Guthion	n		1.0E-02	-----	-----
Heptachlor	y	0.52e	3.8E-03	1.60E-06	1.61E-06
Heptachlor epoxide	y	0.52e	3.8E-03	7.94E-07	7.94E-07
Hexachlorobenzene	y			5.82E-06	5.82E-06
Hexachlorobutadiene	y			1.40E-01	3.73E-01
Hexachlorocyclopentadiene	n			6.32E+01	1.31E+02
Hexachloroethane	y			6.32E-02	6.65E-02
Indeno(1,2,3-cd)pyrene	y			3.20E-04	3.70E-04
Iron (1)	n			3.00E+02	
Isophorone	y			9.46E+00	1.94E+01
Lead (j)	n	6.5E+01	2.5E+00	-----	-----
Malathion	n		1.E-01	-----	-----
Manganese	n			-----	-----
Mercury (m)	n	1.4E+00	1.2E-02	1.1E-03	1.1E-03
Methoxychlor	n		3.E-02	1.65E+00	1.69E+00
Methyl bromide	n			1.35E+01	3.02E+01
2-Methyl-4,6-Dinitrophenol	n			3.12E+00	5.74E+00
Methylene chloride	y			1.95E+00	1.20E+01
Mirex	n		1.E-03	-----	-----
Nickel (j)	n	4.7E+02	5.2E+01	3.14E+01	3.44E+01
Nitrobenzene	n			5.38E+00	1.40E+01
N-Nitrosodimethylamine	y			3.41E-04	6.10E-02
N-Nitrosodi-n-propylamine	y			2.01E-03	1.02E-02
N-Nitrosodiphenylamine	y			1.17E-01	1.21E-01
N-Nitrosopyrrolidine	y			8.24E-03	7.01E-01
Parathion	n	6.5E-02	1.3E-02	----	----
PCB Total	y	2.0E+00	1.4E-02	1.30E-06	1.30E-06
Pentachlorobenzene	n			3.04E-02	3.05E-02
Pentachlorophenol (n)	y	9.1E+00	5.7E+00	4.32E-02	6.13E-02
Phenol	n			8.06E+03	3.47E+04
Pyrene	n			7.01E+01	8.09E+01
Selenium (NTSWQS)	n	2.0E+01	5.E+00	4.29E+01	8.43E+01
Silver (j)	n	3.4E+00		-----	-----
Sulfide - Hydrogen Sulfide	n		2.0E+00	-----	-----
1,1,2,2-Tetrachloroethane	y			4.20E-02	8.09E-02
Tetrachloroethylene	y			5.78E-02	6.65E-02
Thallium	n			4.45E-02	4.62E-02
Toluene	n			1.06E+03	1.51E+03
Toxaphene	y	7.3E-01	2.E-04	5.61E-06	5.62E-06
Tributyltin	n	4.6E-01	6.3E-01	1.73E-03	1.73E-03
1,2,4-Trichlorobenzene	n			6.82E+00	7.10E+00
1,1,2-Trichloroethane	y			1.56E-01	3.15E-01
Trichloroethylene	y			4.22E-01	6.06E-01
2,4,6-Trichlorophenol	y			4.76E-02	4.90E-02
Vinyl chloride	y			8.03E-01	3.98E+00

01039

Compound	*Carcinogen?*	*Acute (a) Criteria*	*Chronic (b) Criteria*	*Water & Organisms*	*Organisms Only*
Zinc (j)	*n*	*1.1E+02*	*1.0E+02*	*4.70E+02*	*5.17E+02*

Footnote 1: The previously approved criterion was removed from Table 1in the 2010 water quality standards revision.

A. Human Health Criteria and Application to Spokane Tribe's Designated Uses

In the Tribe's WQS, each water body is assigned to a particular "Class." Fresh waters are designated as Class AA, Class A, or Lake Class waters. Each "Class" contains a suite of designated uses. A designated use of Class AA protects waters for:

- Primary contact ceremonial and spiritual
- Cultural
- Water supply (domestic, industrial, agricultural)
- Stock watering
- Fish and shellfish, including:
    - Salmonid migration, rearing, spawning, and harvesting.
    - Other fish migration rearing, spawning, and harvesting.
    - Clam, and mussel rearing, spawning, and harvesting.
    - Mollusks, crustaceans and other shellfish rearing, spawning, and harvesting
- Primary contact recreation
- Commerce and navigation

Class A and Lake Class waters are assigned the same designated uses as Class AA, except for the "Clam, mussel rearing, spawning and harvesting" sub-category which is listed under the Fish and shellfish designated use.

Additionally, the tribal standards (Section 10) state that waters not specifically identified as Class AA, A or Lake Class, shall be designated as Class A. Therefore, all tribal waters are protected for fish and shellfish, including harvesting, domestic water supply and recreation.

Furthermore, Section 6 (Toxic Pollutants), provision 9 of the Tribe's WQS states:

> (*9) The criteria in Table 1 shall be applied to all surface waters of the tribe for the protection of aquatic life and human health. The concentration for each compound listed in Table 1 is a criterion for aquatic life or human health protection….*

Table 1 of Section 6 (Toxic Pollutants) in the Tribes WQS provides the human health and aquatic life water quality criteria for toxic pollutants. The Tribe's "water + organism" criteria in Table 1 were established to limit the pollutant to levels that provide for the safe consumption of drinking water and fish. The "organism only" criteria in Table 1 were established to limit the pollutant to levels that provide for the safe consumption of fish and shellfish only; this does not include the consumption of water. The human health and aquatic life criteria apply to all surface waters on the reservation.
For human health protection, EPA recommends that states and tribes apply human health criteria for toxics to all waters with designated uses providing for public water supply protection (and therefore a potential water consumption exposure route), recreation, and/or aquatic life protection (and therefore a

potential fish consumption route).[7] The Tribe's approach is consistent with EPA's recommended approach.

The Tribe's 2010 revised human health criteria for toxic pollutants are developed, for the most part, pursuant to methods presented in EPA's 2000 Human Health Methodology.[8] This methodology protects human health from long-term exposure to toxic pollutants in drinking water and through eating fish containing these pollutants. These criteria take into consideration the cancer potency or systemic toxicity of a pollutant, the exposure related to surface water exposure and a risk characterization. The criteria calculations for non-carcinogens and carcinogens differ depending upon the exposure scenario for which the criteria are derived and are further described below.

EPA reviewed the Tribe's 2010 revised human health criteria for toxic pollutants to assess whether they were consistent with the CWA and its implementing regulations. EPA's evaluation focused on whether the criteria were consistent with 40 CFR § 131.11(a), which states that criteria must be based on sound scientific rationale and contain sufficient parameters or constituents to protect designated uses.

B. Criteria Methodology and Input Variables Used by the Tribe

Pursuant to CWA § 304(a), EPA has published recommended criteria for use by states and tribes in adopting and revising criteria.[9] For human health criteria, the values reflect the "national default" values for the risk assessment parameters provided in the 2000 Human Health Methodology, the reference dose values (RfD) contained in EPA's Integrated Risk Information System[10] (IRIS) at the time of publication, and the use of bioconcentration factors (BCFs) as opposed to site-specific bioaccumulations factors (BAFs).[11] While the 2000 Human Health Methodology provides national default values, it also provides necessary guidance to adjust criteria to reflect local conditions and encourages states and tribes to use the guidance to appropriately reflect local conditions and/or protect identifiable subpopulations.[12] The Tribe revised and adopted human health criteria that were derived, for the most part, using EPA's 2000 Human Health Methodology as well as local fish consumption and drinking water intake rates.

The risk assessment-based procedures EPA puts forth in the 2000 Human Health Methodology are

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[7] EPA 1994. *Water Quality Standards Handbook*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C., EPA-823-B-94-005a. August 1994.

[8] EPA. 2000. *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. EPA 822-B-00-004

[9] EPA National Recommend Ambient Water Quality Criteria for the Protection of Aquatic Life and Human Health. Published pursuant to section 304(a) of the CWA. Available at: http://www.epa.gov/waterscience/criteria/wqctable/index.html.

[10] IRIS is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS program EPA provides the highest quality science-based human health assessments to support the Agency's regulatory activities.

[11] The 2000 Human Health Methodology recommends the use of national BAFs in the calculation of ambient water quality criteria. However, EPA has only provided guidance on the calculation of national BAFs; BAFs have not been calculated for individual pollutants. EPA uses BCFs in their nationally recommended criteria. States and Tribes have the option to use these BCFs or to calculate BAFs using EPA guidance documents. Development of BAFs is time and resource intensive and BAFs can vary from site to site. Thus it is difficult to develop BAFs on a national or statewide scale. Therefore, until BAFs are developed, EPA's national 304(a) human health recommendations continue to be based on the use of BCFs which reflect the uptake and retention of a pollutant by an aquatic organism from water alone (as opposed to a BAF which reflects the uptake of a pollutant from all sources [e.g., ingestion, sediment]).

[12] EPA. 2000. *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. EPA 822-B-00-004. Pages iii, 1-11.

specific to whether the endpoint is cancer or non-cancer. When using cancer as the critical risk assessment endpoint, the criteria are presented as a range of concentrations associated with specified incremental lifetime risk levels.[13] The following briefly provides the key features of each procedure. A simplified version of this equation is provided in Figure 1 below.

Figure 1. Simplified version of the equation used by the Tribe in deriving the human health criteria for carcinogens.

$$AWQC = \frac{(Risk\ Level \bullet BW)}{[CSF \bullet (DI + (FCR \bullet BAF))]}$$

where:

AWQC	=	Ambient Water Quality Criterion (milligrams per liter)
Risk Level	=	Risk level (unitless)
CSF	=	Cancer slope factor (milligrams per kilogram per day)
BW	=	Human body weight (kilograms)
DI	=	Drinking water intake (liters per day)
FCR	=	Fish Consumption Rate (kilograms per day)
BAF	=	Bioaccumulation factor (liters per kilogram)

*Note that criteria calculations for organism only criteria are not shown and can be derived by removing the drinking water intake (DI) term.

When using noncancer effects as the critical endpoint, the criteria reflect an assessment of a "no-effect" level. Criteria for non-carcinogenic pollutants are calculated through an equation that relies on pollutant-specific and general risk-assessment values for each parameter. A simplified version of this equation is provided in Figure 2 below.

[13] EPA's methodology recognizes that states and tribes have the flexibility to adopt human health criteria within a risk level range of 1 X 10^{-6} to 1 X 10^{-5} as long as highly exposed populations would be protected at a minimum of 1X 10^{-4} risk level (i.e., there is a 1:10,000 risk of getting cancer).

Figure 2. Simplified version of the equation used by the Tribe in deriving the human health criteria for non-carcinogens.

$$AWQC = RfD \bullet RSC \bullet \frac{(BW)}{[DI + (FCR \bullet BAF)]}$$

where:

AWQC	=	Ambient Water Quality Criterion (milligrams per liter)
RfD	=	Reference dose for noncancer effects (milligrams per kilogram per day)
RSC	=	Relative source contribution factor to account for non-water sources of exposure (unit less)
BW	=	Human body weight (kilograms)
DI	=	Drinking water intake (liters per day)
FCR	=	Fish Consumption Rate (kilograms per day)
BAF	=	Bioaccumulation factor (liters per kilogram)

*Note that criteria calculations for organism only criteria are not shown and can be derived by removing the drinking water intake (DI) term.

The Tribe's new and revised criteria were derived using the following input variables:

RfD: Most of values the Tribe used were values recommended by EPA in the 2002 and 2003 CWA § 304(a) criteria recommendations.[14, 15] Alternative values used by the Tribe will be discussed in more detail when EPA reviews specific human health criteria.

RSC: Most of the values the Tribe used were values recommended by EPA in the 2002 and 2003 CWA § 304(a) criteria recommendations.[16, 17] Alternative values used by the Tribe will be discussed in more detail when EPA reviews specific human health criteria.

BW: 70 kilograms[18] (value recommended by EPA).

DI: 4 liters per day (value reflects a subsistence lifestyle; EPA's review of the tribal value is presented below in section C).

[14] See: EPA. 2002. *National Recommended Water Quality Criteria 2002 – Human Health Criteria Calculation Matrix*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. EPA 822-R-02-012. Available at: http://www.epa.gov/waterscience/criteria/wqctable/hh_calc_matrix.pdf.

[15] See: EPA. 2003. *National Recommended Water Quality Criteria for the Protection of Human Health*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. *Federal Register*, Volume: 68, Issue: 250, Page: 75507 (68 FR 75507), December 31, 2003. Available at: http://www.epa.gov/fedrgstr/EPA-WATER/2003/December/Day-31/w32211.htm.

[16] See: EPA. 2002. *National Recommended Water Quality Criteria 2002 – Human Health Criteria Calculation Matrix*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. EPA 822-R-02-012. Available at: http://www.epa.gov/waterscience/criteria/wqctable/hh_calc_matrix.pdf.

[17] See: EPA. 2003. *National Recommended Water Quality Criteria for the Protection of Human Health*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. *Federal Register*, Volume: 68, Issue: 250, Page: 75507 (68 FR 75507), December 31, 2003. Available at: http://www.epa.gov/fedrgstr/EPA-WATER/2003/December/Day-31/w32211.htm.

[18] EPA. 2000. *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health*. U.S. Environmental Protection Agency, Office of Water, Washington, D.C. EPA 822-B-00-004. Pages 4-18 to 4-19.

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FCR: 865 grams per day (value reflects a subsistence lifestyle; EPA's review of the tribal value is presented below in section C).

BAF: Most of the values the Tribe used were values recommended by EPA in the 2002 and 2003 CWA § 304(a) criteria recommendations. Alternative values used by the Tribe will be discussed in more detail when EPA reviews specific human health criteria.

Cancer risk level: 1×10^{-6} (value recommended by EPA)

CSF: values provide in EPA's Integrated Risk Information System (IRIS).

Further information regarding each of these variables is available in EPA's 2000 Human Health Methodology.

C. EPA's Review of Fish Consumption Rate and Drinking Water Intake

As described above, the Tribe calculated its human health criteria using several exposure and risk variables, and determined a risk level it deemed acceptable while still protecting the use – in this case, the level of protection provided to consumers of organisms and water taken from the tribal waters to which the criteria apply.

The regulations at 40 CFR § 131.11(a) provide that new or revised criteria "must be based on sound scientific rationale and must contain sufficient parameters or constituents to protect designated uses." However, at the same time, EPA may not disapprove water quality criteria that are more stringent than EPA's CWA section 304(a) criteria solely on the grounds that the proposed criteria are too stringent.[19] While all criteria must be "developed based on scientifically defensible methods," a state or tribe need not justify its policy decision to develop criteria based on stated goals that differ from those underlying EPA's 304(a) recommendations and that, therefore, result in the calculation of more stringent criteria values.[20]

Thus, for the Tribe's criteria that are more stringent than the 304(a) recommendations, EPA evaluated the criteria under the CWA as follows:

- First, EPA acknowledged the Tribe's decision to ensure that its water quality is sufficient to support traditional subsistence practices. Specifically, EPA acknowledged that the selection of the objective to be protected by the criterion is a question of Spokane tribal policy. More generally, EPA noted that the CWA does not require a state or tribe to justify its decision to protect a particular use by establishing that a sufficient number of persons will participate in that use. Neither did the Tribe purport to justify its policy objectives by reference to the number of persons who currently rely on tribal waters for subsistence purposes.
- Second, EPA evaluated the scientific defensibility of the assumptions and methodology the Tribe used in deriving criteria to protect its water quality goals, including the derivation of fish

[19] EPA's established interpretation of its regulations reflects that they must be understood consistent with the statutory limits on EPA's review authority under the CWA. See 56 FR 64885-6 (1991) (recognizing, in light of CWA § 510, that EPA "may not disapprove either Tribal or State standards solely on the grounds that the standard is too stringent").
[20] Id.

consumption and drinking water rates characteristic of the Spokane Tribe's subsistence traditions.

- Third, EPA evaluated whether the Tribe's criteria are sufficient to protect not only 304(a) fishable/swimmable goals, but also the Tribe's goal that tribal water quality be sufficient to support the traditional subsistence lifestyle.

As stated above, the Tribe generally relied on EPA's 2000 Human Health Methodology to derive human health criteria. The Tribe applied that methodology using EPA recommended default values, except for the specific variables for the specific pollutants discussed in Section V.D.3, 4 and 5 (below).

The 2000 Human Health Methodology allows states and tribes flexibility by providing scientifically valid options for developing criteria based on local or regional fish consumption rates. The 2000 Human Health Methodology suggests the following preference hierarchy for the data to be used in determining fish consumption rates: (1) local data, (2) data reflecting similar geography/population groups, (3) data from national surveys, and (4) EPA's default intake rates.

Traditional Lifestyle Studies

To implement its policy choice to develop water quality standards that protect traditional subsistence practices, the Tribe determined fish and drinking water consumption rates corresponding to traditional diet and cultural practices specific to the Spokane Reservation, using sources that were summarized as part of an exposure assessment,[21] as confirmed by traditional knowledge obtained from tribal members.

According to those sources, the Reservation is located at the confluence of the Spokane and Columbia Rivers. It is an arid region that is fairly pristine and undeveloped. It currently provides enough resources for some members to continue a traditional subsistence dietary lifestyle, and for all members to obtain traditional foods. The traditional lifestyle is governed by the seasons. Hunting, fishing, and gathering support nutritional, cultural, spiritual, and medicinal needs of the tribal members. Among families engaged in a subsistence lifestyle, the family members work in the field on a regular basis to keep the extended family unit stocked with a wide variety of plants and wildlife. While in the field, a subsistence consumer lives off the land by consuming surface and spring water, fish, wild plants and wildlife. In addition to time spent in hunting, fishing, or gathering, time is spent cleaning, processing, and preserving hides, drying vegetal food or medicines, and making a wide variety of items. A subsistence lifestyle (except for infants) involves participating in daily sweat lodge throughout the year. Based on these activities, the caloric needs of a tribal member range from 2,000 to 4,000 kilocalories (kcal) per day for adult males, depending on the level of activity, with 2,500 to 3,000 kcal representing a moderately active traditional outdoor lifestyle for tribal members.

Tribal Fish Consumption Rate

The Tribe uses a fish consumption rate of 865 g/d. The article by Harper et al. reviewed studies of the mid-Columbia River Indians and found that the original Spokane diet was based on salmon and included large and small game, roots, berries, and other plants. One study indicated that traditionally, 45% of the native Columbia Plateau dietary calories came from fish and game, with higher estimates for upriver tribes such as the Spokane Tribe.[22] Another study found that the most robust estimate of the salmon

[21] Harper, B.L., Flett B., Harris S., Abeyta C., Kirschner F. 2002. *TheSpokane Tribe's Multipathway Subsistence Exposure Scenario and Screening Level RME.* Society for Risk analysis, Risk Analysis Vol. 22. No. 3.

[22] Hunne, E.S. 1990. *Nch'i-Wana, The Big River: Mid-Columbia Indians and Their Land.* Seattle, WA: University of Washington Press.

intake by the Spokane Tribe was the "Walker estimate" of approximately 1,200 pounds per year,[23] which translates to approximately 1,492 g/d.[24] The Harper article concluded that this consumption rate would translate to 2,566 kcal/day from consumption of fish in estuaries (prior to migration).[25] The Harper article stated that the caloric content of salmon was reduced by about 1/3 after migrating to the Spokane area, resulting in approximately 1,600 kcal/day from fish (2,566 X 0.64).

The Harper article next sought to estimate an appropriate high fish diet for a tribal member practicing a traditional lifestyle today, as opposed to the estimate of historical consumption discussed above. The authors assumed that approximately 80 percent of a traditional diet today would be similar to a historical native diet. Based on this assumption caloric intake from fish would be approximately 1,300 kcal/d (0.8 × 1,600 kcal/day).[26] Furthermore, due to the construction of the Grand Coulee Dam, the anadromous fish runs have been destroyed, so there has been a shift in diet to Kokanee (land-locked sockeye salmon), Dolly varden, rainbow trout, whitefish, mussels, crayfish, and other species. The authors assumed a caloric content for sockeye salmon of 400 kcal/275 g. This would translate into a fish consumption rate of approximately 890 g/d, in order to maintain the caloric intake characteristic of a traditional subsistence lifestyle, given the fish currently available (1,300 kcal/d × 275g/400kcal).

Based on all of the above factors, as well as interviews with tribal members, Harper et al. estimated that a fish consumption rate of 885 g/d would be the realistic high fish consumption rate for the Spokane Tribe. The Tribe's proposed criteria are based on a fish consumption rate of 865 g/d, which is slightly lower than this estimated "high" rate, and well within the accuracy of the estimation methodology.

Tribal Drinking Water

The Tribe's criteria are also based on a drinking water intake rate of 4 L/d. The drinking water intake rate (DI) for the Confederated Tribes of the Umatilla Indian Reservation (CTUIR), 3 L/d for adults, was used as a starting point to determine the drinking water intake rate for the Spokane Tribe since the CTUIR reservation is also located in an arid region, and the DI was based on the water intake needs of a person engaged in the traditional lifestyle.[27] The CTUIR rate estimates an average intake rate based on interviews with CTUIR tribal members. The CTUIR intake rate is based on using 1L of water consumed at the home, 1L of water consumed from home to worksite, and 1L of water consumed at the worksite (i.e., field where tribal member live off the land and consume surface and spring water). In addition to the above activities, the traditional lifestyle for a Spokane Tribal member includes daily use of a sweat lodge for several hours. The Harper article estimated that an additional 1 L of water is needed to re-hydrate after using the sweat lodge, resulting in the assumed intake rate of 4 L/day.

SUMMARY

As discussed above, the Tribe's estimates of the fish consumption and water intake rates for a traditional subsistence lifestyle were based on (1) open peer-reviewed literature, (2) ethnographic documents and reports concerning traditional lifestyles and practices, and (3) confirmatory statements from tribally

[23] Scholz, A, O'Laughlin, K., Geist, D., Peone, D., Uehara, J., Fileds, L., Kleist, T., Zozaya, I., Peone, T., and Teesatuskie, K., 1985. *Compilation of Information on Sal mon and Steelhead Total Run Size, Catch, and Hydropower Related Losses in the Upper Columbia River Basin, Above Grand Coulee Dam. Fisheries Technical Report No. 2., Upper Columbian United Tribes Fisheries Center.* Cheney, WA:Eastern Washington University Department of Biology.

[24] 1,200 lb/yr X 454 g/lb ÷ 365.24 days/yr.

[25] Harper et al., p 518.

[26] The authors also tried to approximate the historic dietary balance which found that approximately 45% of caloric intake was from fish, and concluded that, based on a calorie intake of 2,500 to 3,000 kcal/day, this provided further support for a fish consumption intake rate of approximately 1,300 kcal/d.

[27] Harris, S.G. and Harper, B.L. 1997. A native American Exposure Scenario. *Risk Analysis,* 17: 789 – 785.

recognized cultural experts whose expertise derives from their traditional environmental knowledge. EPA concludes the FCR used by the tribe corresponds to obtaining approximately 2,000 to 4,000 kcal/day under subsistence conditions, around tribal lands. EPA also concludes that this estimate of caloric input could correspond to physiological needs while undertaking the subsistence lifestyle described. Finally, historical and ethnographic reports corroborate that the subsistence lifestyle described accurately corresponds to the traditional practices of the Spokane Tribe. EPA also believes a drinking water intake of 4L/d could be representative of the subsistence lifestyle in an arid environment with daily sweat lodge use.

D. EPA Action on New and Revised Human Health Criteria

1. EPA Approval Action on 160 Revised Human Health Criteria

The Tribe has developed and adopted 160 human health criteria using EPA's 2000 Human Health methodology, a fish consumption rate of 865 g/d, a drinking water intake of 4 L/d, and values for RfD, RSC, BW, BAF, CSF and risk level that are consistent with the default values that EPA utilized in deriving its national CWA § 304(a) human health criteria guidance values. The following table contains the 160 human health criteria:

Table 1: Human Health Criteria for Toxics (µg/L)

Compound	*Carcinogen?*	*Water & Organisms*	*Organisms Only*
Acenaphthene	*n*	*1.97E+01*	*2.01E+01*
Acrolein	*n*	*5.75E+00*	*5.87E+00*
Acrylonitrile	*n*	*4.33E-03*	*5.00E-03*
Aldrin (e)	*y*	*1.02E-06*	*1.02E-06*
Anthracene	*n*	*7.01E+02*	*8.09E+02*
Arsenic (h)	*n*	*9.51E-04*	*1.05E-03*
Benz(a)anthracene	*y*	*3.2E-04*	*3.7E-04*
Benzene	*y*	*2.84E-01*	*5.37E-01*
Benzidine	*y*	*3.82E-06*	*4.02E-06*
Benzo(a)pyrene	*y*	*3.2E-04*	*3.7E-04*
3,4-Benzo(b)fluoranthene	*y*	*3.2E-04*	*3.7E-04*
Benzo(k)fluoranthene	*y*	*3.2E-04*	*3.7E-04*
alpha BHC	*y*	*9.54E-05*	*9.88E-05*
beta BHC	*y*	*3.34E-04*	*3.46E-04*
Bis(2-chloroethyl) Ether	*y*	*6.38E-03*	*1.07E-02*
Bis(2-chloroisopropyl) Ether	*n*	*4.56E+02*	*1.31E+03*
Bis(2-chloromethyl)ether	*y*	*7.00E-05*	*5.84E-04*
Bis(2-ethylhexyl)phthalate	*y*	*4.29E-02*	*4.45E-02*
Bromoform	*y*	*1.22E+00*	*2.73E+00*
Butylbenzyl phthalate	*n*	*3.87E+01*	*3.91E+01*
Carbon tetrachloride	*y*	*2.66E-02*	*3.32E-02*
Chlorodibromomethane	*y*	*1.15E-01*	*2.57E-01*
Chloroform	*y*	*1.58E+00*	*3.54E+00*
2-Chloronaphthalene	*n*	*3.13E+01*	*3.20E+01*
2-Chlorophenol	*n*	*2.92E+00*	*3.02E+00*

Compound	Carcinogen?	Water & Organisms	Organisms Only
Chrysene	y	3.20E-04	3.70E-04
4,4'-DDD	y	6.29E-06	6.29E-06
4,4'-DDE	y	4.44E-06	4.44E-06
4,4'-DDT	y	4.44E-06	4.44E-06
Dibenz(a,h)anthracene	y	3.20E-04	3.70E-04
Dibutyl phthalate	n	8.64E+01	9.09E+01
1,3-(m)Dichlorobenzene	n	1.80E+01	1.95E+01
3,3-Dichlorobenzidine	y	5.68E-04	5.76E-04
Dichlorobromomethane	y	1.56E-01	3.48E-01
1,2-Dichloroethane	y	1.53E-01	7.41E-01
2,4-Dichlorophenol	n	5.36E+00	5.96E+00
1,2-Dichloropropane	n	1.40E-01	2.97E-01
Dieldrin (e)	y	1.08E-06	1.08E-06
Diethyl phthalate	n	8.34E+02	8.87E+02
2,4-Dimethylphenol	n	1.64E+01	1.73E+01
Dimethyl phthalate	n	1.99E+04	2.25E+04
2,4-Dinitrophenol	n	2.64E+01	1.08E+02
2,4-Dinitotoluene	y	3.06E-02	6.78E-02
2,3,7,8-TCDD (Dioxin)	y	1.04E-10	1.04E-10
1,2-Diphenylhydrazine	y	3.43E-03	4.06E-03
alpha Endosulfan	n	1.77E+00	1.80E+00
beta Endosulfan	n	1.77E+00	1.80E+00
Endosulfan sulfate	n	1.77E+00	1.80E+00
Endrin aldehyde	n	6.11E-03	6.12E-03
Fluoranthene	n	2.80E+00	2.81E+00
Fluorene	n	9.35E+01	1.08E+02
Heptachlor	y	1.60E-06	1.61E-06
Heptachlor epoxide	y	7.94E-07	7.94E-07
Hexachlorobenzene	y	5.82E-06	5.82E-06
Hexachlorobutadiene	y	1.40E-01	3.73E-01
Hexachloroethane	y	6.32E-02	6.65E-02
Indeno(1,2,3-cd)pyrene	y	3.20E-04	3.70E-04
Isophorone	y	9.46E+00	1.94E+01
Methyl bromide	n	1.35E+01	3.02E+01
2-Methyl-4,6-Dinitrophenol	n	3.12E+00	5.74E+00
Methylene chloride	y	1.95E+00	1.20E+01
Nickel	n	3.14E+01	3.44E+01
Nitrobenzene	n	5.38E+00	1.40E+01
N-Nitrosodimethylamine	y	3.41E-04	6.10E-02
N-Nitrosodi-n-propylamine	y	2.01E-03	1.02E-02
N-Nitrosodiphenylamine	y	1.17E-01	1.21E-01
N-Nitrosopyrrolidine	y	8.24E-03	7.01E-01
PCB Total	y	1.30E-06	1.30E-06
Pentachlorobenzene	n	3.04E-02	3.05E-02
Pentachlorophenol	y	4.32E-02	6.13E-02
Phenol	n	8.06E+03	3.47E+04
Pyrene	n	7.01E+01	8.09E+01

Compound	*Carcinogen?*	*Water & Organisms*	*Organisms Only*
Selenium (NTSWQS)	*n*	*4.29E+01*	*8.43E+01*
1,1,2,2-Tetrachloroethane	*y*	*4.20E-02*	*8.09E-02*
Tetrachloroethylene	*y*	*5.78E-02*	*6.65E-02*
Toxaphene	*y*	*5.61E-06*	*5.62E-06*
1,1,2-Trichloroethane	*y*	*1.56E-01*	*3.15E-01*
Trichloroethylene	*y*	*4.22E-01*	*6.06E-01*
2,4,6-Trichlorophenol	*y*	*4.76E-02*	*4.90E-02*
Zinc	*n*	*4.70E+02*	*5.17E+02*

EPA Action
In accordance with its CWA, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the Tribe's revised human health toxic criteria for the 160 human health criteria listed in Table 1 above.

EPA Rationale
EPA's WQS regulations at 40 CFR Part 131 require that criteria protect the designated uses. As noted previously, the Tribe's human health criteria apply to all waters on the reservation, including those protected for fishing, water supply, and recreation uses and, thus, must be established at a level that will protect those uses. Therefore, EPA must evaluate whether the criteria protect the Tribe's human health uses.

EPA's 2000 Human Health Methodology provides guidance for deriving human health criteria for toxic pollutants. For each variable used in the criteria calculation, EPA provides a "national default value" and guidance on specific adjustments that may be necessary to reflect local conditions and/or protect identifiable subpopulations. As part of evaluating whether the Tribe's criteria protect the designated uses, EPA looked at the input values used by the Tribe and whether there was Tribal-specific information relative to each value that should be considered in the review. When calculating the criteria in Table 1, the Tribe used EPA's national default values for all inputs except the FCR and DI. As discussed above, EPA has found that the Tribe has appropriately considered local and regional data, (relevant to an objective that was within the Tribe's policy discretion to protect) when selecting input variables for the FCR and DI.

The 2000 Methodology document provides an extensive technical basis and justification as to how EPA's recommended human health criteria and methodology adequately protect human health uses. The Tribe's human health criteria identified in Table 1 were developed consistent with these recommendations, therefore, EPA has determined that these criteria protect human health uses in accordance with 40 CFR § 131.11(a)(1).

In any future updates the Tribe makes to its human health criteria, EPA recommends the Tribe consider using an RSC value of 0.2, or an appropriate alternative up to 0.8, rather than 1 when calculating non-carcinogen criteria.

2. EPA Disapproval of the Deletion of Asbestos Human Health Criterion

In 2003, the Tribe adopted an asbestos criterion (7 MFL) for the protection of human health into Table 1 of their water quality standards. The water quality standards specifically state that the criteria in Table 1 are for the protection of human health. Additionally, the Tribe adopted the same asbestos criterion (7 MF/L) into Table 2 of their water quality standards for the protection of primary contact ceremonial

uses. Many of the criteria in Table 2 are higher than the concentrations necessary to protect human health so it is not clear that the criteria in Table 2 were established to protect human health. In the 2010 water quality standards revision, the Tribe removed the water and organisms human health criterion for asbestos (7 MF/L) from Section 6, Table 1 of their water quality standards. However, the asbestos criterion in Table 2 was retained.

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's removal of the water and organisms human health toxic criteria for asbestos from Table 1 of the Tribe's water quality standards.

EPA Rationale
As discussed previously, for human health protection, EPA recommends that states and tribes apply human health criteria for toxics to all waters with designated uses providing for public water supply protection (and therefore a potential water consumption exposure route), recreation, and/or aquatic life protection (and therefore a potential fish consumption route). Asbestos is a priority pollutant and EPA's 304(a) recommendation for the protection of human health (water and organisms) is 7 MF/L.
While the Tribe has retained an asbestos criterion in Table 2, it is not clear that Table 2 criteria are intended to protect human health or aquatic life. Given the lack of clarity of the intended level of protection in Table 2, EPA does not view this Table as providing the same level of protection for human health as Table 1.

The Tribe has not provided any rationale to show that removing the asbestos criterion from Table 1will still result in the protection of human health; therefore, EPA is disapproving the removal of the human health (water and organism) asbestos criterion from Table 1.

Remedy to Address EPA Disapproval
To address this disapproval, the Tribe must adopt human health criteria that are based on a sound scientific rationale and protect human health uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- Adopt EPA's 304(a) recommendation for human health (water and organisms) of 7 MF/L into Table 1.
- Provide a sound scientific rationale to establish that an asbestos criterion is not necessary for the protection of human health uses.
- Develop an alternative human health criterion for the consumption of water and organisms and provide a sound scientific justification to establish that it is protective of human health uses.

3. EPA Disapproval Action for Dichlorodiflouromethane Human Health Criteria

The Tribe revised their human health criteria for dichlorodifluoromethane to the following:

Table 2. Human Health for Toxic Pollutants (µg/L)

Compound	*Carcinogen?*	*Water & Organisms*	*Organisms Only*
Dichlorodiflouromethane	*n*	*1.93E+03*	*4.32E+03*

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revised human health toxic criteria for the dichlorodifluoromethane human health criteria listed in Table 2 above.

EPA Rationale
EPA's WQS regulations at 40 CFR Part 131 require that criteria protect the designated uses. As noted previously, the Tribe's human health criteria apply to all waters on the reservation, including those protected for fishing, water supply and recreational uses and thus must be established at a level that will protect those uses. Therefore, EPA must evaluate whether the criteria protect the Tribe's human health uses.

The Tribe used EPA's 2000 Human Health Methodology to develop the human health criteria for dichlorodifluoromethane. As part of evaluating whether the Tribe's criteria protect the designated uses, EPA looked at the input values used by the Tribe and whether there was adequate scientific information to support the use of each value.

For dichlorodifluoromethane the Tribe used the equations for non-carcinogens to develop the human health criteria. The following variables were used:

RfD = 0.2 mg/kg/d	RSC = 1	BW = 70 kg
DI = 4 L/d	FCR = 865 g/d	BAF = 3.75 L/kg

The values the Tribe used for RfD, BW, DI, FCR are consistent with EPA recommendations. The Tribe has not provided any scientific information to support the use of the non-carcinogen equations, or for the values used for the BAF or RSC. Additionally, in EPA's *Ambient Water Quality for Halomethanes* (EPA 440/5-80-051, October 1980) dichlorodifluoromethane was treated as a carcinogen.

Criteria must be based on sound scientific rationale and contain sufficient parameters or constituents to protect designated uses. The Tribe has not provided supporting documentation to show that the values used for the RSC and BAF are based on sound science and will be protective of human health or if using the non-carcinogen equation is appropriate. Therefore, EPA is disapproving the human health criteria for dichlorodifluoromethane.

Remedies to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt human health criteria that are based on a sound scientific rationale and protect human health uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- EPA has not developed human health criteria for dichlorodifluoromethane using the 2000 Human Health Methodology. For a pollutant for which EPA has published a recommended Section 304(a) water quality criterion based on the 1980 Methodology and for which EPA has not promulgated a Maximum Contaminant Level Goal[28] (MCLG), EPA recognizes the current Section 304(a) water

[28] The MCLG is the level of a contaminant in drinking water below which there is no known or expected risk to health. EPA does not recommend using MCLs which are set as close to MCLGs as feasible using the best available treatment technology and taking cost into consideration.

quality criterion (see 65 FR 66450). Therefore, the Tribe may use EPA's 1980 human health criteria developed in October 1980 (*Ambient Water Quality Criteria for Halomethanes*, EPA 440/5-80-051).

- Resubmit the previously adopted human health criteria with a sound scientific rationale to establish that the use of the non carcinogen equation and the application of the input values are protective of human health uses.

4. EPA Disapproval Action for Mercury Human Health Criteria

The Tribe revised their human health criteria for mercury to the following:

Table 3. Human Health for Toxic Pollutants (µg/L)

Compound	*Carcinogen?*	*Water & Organisms*	*Organisms Only*
Mercury	*n*	*1.1E-03*	*1.1E-03*

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revised human health toxic criteria for mercury listed in Table 3 above.

EPA Rationale
EPA's WQS regulations at 40 CFR Part 131 require that criteria protect the designated uses. As noted previously, the Tribe's human health criteria apply to all waters on the reservation, including those protected for fishing, water supply and recreational uses and thus must be established at a level that will protect those uses. Therefore, EPA must evaluate whether the criteria protect the Tribe's human health uses.

The Tribe used EPA's 2000 Human Health Methodology to develop the human health criteria for mercury. As part of evaluating whether the Tribe's criteria protect the designated uses, EPA looked at the input values used by the Tribe and whether there was adequate scientific information to support the use of each value.

For mercury, the Tribe used the equations for non-carcinogens to develop the human health criteria. The following variables were used:

RfD = 0.0001 mg/kg/d	RSC = 1	BW = 70 kg
DI = 4 L/d	FCR = 865 g/d	BAF = 7343 L/kg

The values the Tribe used for RfD, BW, DI, FCR are consistent with EPA recommendations.

The BAF value is the Practical Bioconcentration Factor (PBCF, weighted average) used to develop human health criteria for mercury in California waters (see 62 FR 42179).[29] The value used is based on a weighted average of the amount of fish eaten from fresh waters, estuarine-coastal waters, and open oceans.

[29] The PCBFs were derived in 1980 and are: 5500 for fresh water, 3765 for estuarine-coastal waters, and 9000 for open oceans (see pages C-100-1 of *Ambient Water Quality Criteria for Mercury* (EPA 440/5-80-058)). A weighted average is calculated to take into account the average consumption from the three waters.

EPA's current 304(a) guidance recommends methylmercury be expressed as a fish tissue concentration. It was calculated using the criterion equation in the 2000 Human Health Methodology. The equation was rearranged to result in a protective concentration in fish tissue rather than water (see *Water Quality Criterion for the Protection of Human Health: Methylmercury*, EPA-823-R-01-001, January 2001).

The Tribe may adopt a water column number for mercury, however, the criteria must be based on sound scientific rationale and contain sufficient parameters or constituents to protect designated uses. The Tribe's submission lacked supporting documentation to show that the values used for the RSC and BCF are based on sound science and will be protective of human health. For example, the Tribe has not provided information to show that the PBCF on tribal land is similar to that of California. Therefore, EPA is disapproving the human health criteria for mercury.

Remedies to Address EPA's Disapproval

To address this disapproval, the Tribe must adopt human health criteria that are based on a sound scientific rationale and protect human health uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- EPA used the 2000 Human Health Methodology to develop a 304(a) criterion for methylmercury and expressed the criterion as a fish tissue value (mg/kg). The Tribe may adopt EPA's current 304(a) recommendation for methylmercury fish tissue (as modified by the Tribal fish consumption rate), and implement it without water column translation; or adopt a water column concentration, using the translation methodologies outlined in section 3.1.3.1 of EPA's *Guidance for Implementing the January 2001 Methylmercury Water Quality Criterion* (EPA 823-R-10-001, April 2010); or use a combination of the above two approaches. For example, the Tribe could adopt a fish tissue criterion and implement it without water column translation in some waters and with water column translation in other waters.

  Site specific data for translating the fish tissue criterion to water column concentration, where needed, will take time to collect. Therefore, the Tribe should consider retaining their existing water column criteria (or adopting an updated water column criterion which reflects their new fish consumption rate), on a temporary basis, particularly for waters where there is a relatively high direct water input of mercury. In such a case where the tribe has retained the existing water column criteria, permits include both a limit based on the numeric water column criterion and other requirements based on the fish tissue criterion (see Chapter 7 of EPA's *Guidance for Implementing the January 2001 Methylmercury Water Quality Criterion*).

- Resubmit the previously adopted human health criteria with a sound scientific rationale to establish that the application of input values is protective of human health uses.

5. EPA Disapproval Action of 45 New and Revised Human Health Criteria

The Tribe has developed and adopted 45 human health criteria using EPA's 2000 Human Health methodology, a fish consumption rate of 865 g/d, a drinking water intake of 4 L/d, and values for BW, CSF, and risk level that are consistent with the default values that EPA used in deriving its national CWA § 304(a) human health criteria guidance values. However, the Tribe used values for the RfD,

RSC, and/or BAF(BCF) that were not consistent with the default values that EPA used in deriving its national CWA § 304(a) human health criteria guidance values, and the Tribe did not explain how these values were derived. The following table contains these 45 human health criteria:

Table 4. Human Health for Toxic Pollutants(µg/L)

Compound	*Carcinogen?*	*Water & Organisms*	*Organisms Only*
Antimony	*n*	*5.76E+00*	*3.24E+01*
gamma BHC	*y*	*4.53E-04*	*4.69E-04*
Chlordane	*y*	*4.41E-06*	*4.41E-06*
Chlorobenzene	*n*	*1.08E+02*	*1.57E+02*
Cyanide	*n*	*2.88E+02*	*1.62E+03*
1,2-(o)Dichlorobenzene	*n*	*1.21E+02*	*1.31E+02*
1,4-(p)Dichlorobenzene	*n*	*1.80E+01*	*1.95E+01*
1,2-trans-Dichloroethylene	*n*	*2.61E+02*	*1.02E+03*
1,1-Dichloroethylene	*y*	*1.32E-02*	*2.41E-02*
1,3-Dichloropropylene	*n*	*3.72E+00*	*1.27E+01*
Endrin	*n*	*6.11E-03*	*6.12E-03*
Ethylbenzene	*n*	*1.92E+02*	*2.16E+02*
Hexachlorocyclopentadiene	*n*	*6.32E+01*	*1.31E+02*
Thallium	*n*	*4.45E-02*	*4.62E-02*
Toluene	*n*	*1.06E+03*	*1.51E+03*
1,2,4-Trichlorobenzene	*n*	*6.82E+00*	*7.10E+00*
Vinyl chloride	*y*	*8.03E-01*	*3.98E+00*
Cadmium	*n*	*8.75E+00*	---
Chlorine	*n*	*1.75E+03*	---
Chlorpyrifos	*n*	*5.25E+01*	---
Chromium III	*n*	*2.63E+04*	---
Chromium VI	*n*	*5.25E+01*	---
Copper	*n*	*1.21E+01*	*1.21E+01*
Methoxychlor	*n*	*1.65E+00*	*1.69E+00*
Tributyltin	*n*	*1.73E-03*	*1.73E-03*

EPA Action

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revised human health toxic criteria for the 45 human health criteria listed in Table 4 above.

EPA Rationale

EPA's WQS regulations at 40 CFR Part 131 require that criteria protect the designated uses. As noted previously, the Tribe's human health criteria apply to all waters on the reservation, including those protected for fishing, water supply, and recreational uses and, thus, must be established at a level that will protect those uses. Therefore, EPA must evaluate whether the criteria protect the Tribe's human health uses.

As part of evaluating whether the Tribe's criteria protect the designated uses, EPA looked at the input values used by the Tribe and whether there was Tribal-specific information relative to each value that should be considered in the review. The Tribe used some of the EPA's "national default values" but EPA found that the Tribe did not appropriately consider data in selecting some input variables for use in

deriving the criteria identified in Table 4 above. Specifically, the Tribe used input variables for the RfD, RSC, CSF and BAF without providing sufficient scientific support for the values used.
The following tables show the input values that the Tribe used and the values that EPA recommends.

Table 5: CSF Value Used in Developing Human Health Criteria

Compound	*CSF*	
	EPA recommended value	*Value Used by Tribe*
Chlordane	0.35	1.3
gamma BHC (Lindane)	See Footnote 1	1.3
1,1-Dichloroethylene	See Footnote 1	0.6
1,3-Dichloropropylene	0.1	Not used, see footnote 2
Vinyl chloride	1.4	0.0174
1. The Tribe calculated gamma BHC and 1,1 dichlorethylene using the carcinogen equations, however these parameters are non-carcinogens, therefore a CSF value is not used when developing the criteria. 2. The Tribe calculated 1,3-Dichloroprpylene using the non-carcinogen equations. The parameter is a carcinogen and the equations for carcinogens should have been used to calculate the criteria.		

Table 6: RfD Value Used in Developing Human Health Criteria

Compound	*RfD*	
	EPA recommended value	*Value Used by Tribe*
gamma BHC (Lindane)	0.0047	No value used
1,1-Dichloroethylene	0.05	No value used
1,3-Dichloropropylene	See Footnote 1	0.0003
Hexachlorocyclopentadiene	0.006	0.007
Chlorpyrifos	See Footnote 2	0.003
Copper	See Footnote 2	0.15
Cyanide	0.0006	0.02
Toluene	0.08	0.2
1. 1,3 dichloropropylene is a carcinogen therefore an RfD is not used when calculating the criterion. 2. Data is not available to calculate an RfD.		

01055

Table 7: RSC value Used in Developing Human Health Criteria

Compound	*RSC*	
	EPA recommended value	*Value Used by Tribe*
Antimony	0.4	1
gamma BHC (Lindane)	0.2 – 0.8	1
Chlorobenzene	0.2	1
Cyanide	0.2	1
1,2-(o)Dichlorobenzene	0.2	1
1,4-(p)Dichlorobenzene	0.2	1
1,2-trans-Dichloroethylene	0.2	1
1,1-dichloroethylene	0.2	1
Endrin (e)	0.2	1
Ethylbenzene	0.2	1
Hexachlorocyclopentadiene	0.2	1
Thallium	0.2	1
Toluene	0.2	1
1,2,4-Trichlorobenzene	0.2	1
Cadmium	0.25[1]	1
Chlorine	0.2	1
Chlorpyrifos	0.2	1
Chromium III	0.2	1
Chromium VI	0.2	1
Copper	0.2	1
Methoxychlor	0.2	1
Tributyltin	0.2	1
1. RSC is based on the RSC used to develop the cadmium drinking water MCLG.		

Table 8: BAF Used in Developing Human Health Criteria

Compound	*BAF*	
	EPA recommended value	*Value Used by Tribe*
Cadmium	See Footnote 1	0
Chlorine	See Footnote 1	0
Chlorpyrifos	See Footnote 1	0
Chromium III	See Footnote 1	0
Chromium VI	See Footnote 1	0
Copper	See Footnote 1	0
Methoxychlor	See Footnote 2	240
Tributyltin	See Footnote 1	14000
1. EPA does not have data to form a basis for a recommendation and the tribe has not provided any information to support the values used. 2. 8,963 L/kg for tropic level 2, 8860 L/kg for trophic level 3, and 9,001 L/kg for trophic level 4.		

01056

The water quality standards regulations at 40 CFR § 131.11(a) state that new or revised criteria must be based on a sound scientific rationale and contain sufficient parameters or constituents to protect designated uses. To ensure the Tribe's criteria are consistent with this requirement, EPA evaluated the appropriateness of the variables used by the Tribe in deriving its criteria: specifically, whether the variables were based on sound science and led to criteria that would protect human health endpoints consistent with the designated uses of tribal waters. The 2000 Human Health Methodology provides an extensive technical basis and justification as to how EPA's recommendations adequately protect human health. Each of the criteria identified in Table 4 of the Tribe's submission lacked the supporting documentation to show that one or more of the variables (identified in Tables 5 through 8) used to develop the criteria are based on sound science and lead to criteria that are protective of human health uses. Therefore, EPA is disapproving each of the human health criteria contained in Table 4.

Remedies to Address EPA's Disapproval

To address this disapproval, the Tribe must adopt human health criteria that are based on a sound scientific rationale and protect human health uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- For the following parameters, the Tribe may revise the water and organisms and the organisms only human health criteria by incorporating the input values recommended in EPA's 304(a) guidance, as shown below.

Antimony:	RSC = 0.4
Gamma BHC (Lindane):	RfD = 0.0047, use non-carcinogen equations, RSC = 0.2, or an appropriate alternative up to 0.8
Chlordane:	CSF = 0.35
Chlorobenzene:	RSC = 0.2
Cyanide:	RfD = 0.0006, RSC = 0.2
1,2-(o)Dichlorobenzene:	RSC = 0.2
1,4-(p)Dichlorobenzene:	RSC = 0.2
1,2-trans-Dichloroethylene:	RSC = 0.2
1,1-Dichloroethylene:	RfD = 0.05, RSC = 0.2, use non-carcinogen equations
1,3-Dichlorpropylene	CSF = 0.1, risk level = 1×10^{-6}, use carcinogen equations
Endrin:	RSC = 0.2
Ethylbenzene:	RSC = 0.2
Hexachlorocyclopentadiene:	RfD = 0.006, RSC = 0.2
Thallium:	RSC = 0.2
Toluene:	RfD = 0.08, RSC = 0.2
1,2,4 Trichlorobenzene:	RSC = 0.2
Vinyl chloride:	CSF = 1.4

- For the human health criteria associated with **cadmium, copper, chromium III, and chromium VI**: EPA is in the process of developing draft BAFs values for these parameters and expects to have these drafts values available by the beginning of 2014. When these draft values are available, the Tribe may use this information to update their HH criteria for these parameters.

- For the human health criteria associated with **methoxychlor**, the following BAFs may be used when developing the human health criteria: 8,963 L/kg for trophic level 2, 8860 L/kg for trophic level 3, and 9,001 L/kg for trophic level 4.

01057

- The Tribe may resubmit the previously adopted human health criteria for any of the 45 pollutants listed in Table 4 with a sound scientific rationale to establish that the application of each input value is protective of human health uses. Alternatively, the Tribe may re-evaluate any of the criteria to determine if the criterion is necessary for the protection of human health uses on the reservation.

VI. AQUATIC LIFE CRITERIA

A. EPA Action on Freshwater Acute and Chronic Aquatic Life Criteria for Ammonia

In the 2010 water quality standards adoption, the Tribe sought to correct mistakes for its aquatic life ammonia criteria. The ammonia criteria were initially adopted into Table 1 of the Tribe's water quality standards in 2003. The ammonia values adopted in 2003 were expressed in µg/L (rather than mg/L) and two footnotes were referenced (f and g) which provide the equations used to develop the values in the table below. The 2003 values were:

Compound	*Carcinogen?*	*Acute (a) Criteria*	*Chronic (b) Criteria*	*Water & Organisms*	*Organisms Only*
Ammonia (f, g)	*n*	*24.1*	*4.15*	-----	-----

In the 2010 adoption the ammonia values are still expressed in µg/L but the following changes were made (new language is underlined):

Compound	*Carcinogen?*	*Acute (a) Criteria*	*Chronic (b) Criteria*	*Water & Organisms*	*Organisms Only*
Ammonia, <u>unionized</u> (f, g)	*n*	*<u>2.4E+04</u>*	*<u>5.9E+03</u>*	-----	-----

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revisions to the freshwater acute and chronic aquatic life ammonia criteria.

EPA Rationale
In 2003, the Tribe adopted the EPA's 1999 304(a) recommendations for freshwater acute and chronic aquatic life criteria for ammonia. The 1999 recommendations were the most recent 304(a) recommendation when the Tribe adopted their water quality criteria. In 2003, the Tribe adopted the correct equations into footnotes f and g, however, they incorrectly identified the metric associated with the criteria as µg/L rather than mg/L.

The Tribe sought to correct this error in their 2010 water quality standards adoption. However, in trying to correct the error several other errors were made, including the following:

(1) The form of ammonia was changed from total ammonia to un-ionized ammonia. This change effectively increased the allowable amount of un-ionized ammonia (the more toxic form of

ammonia) than was recommended by EPA's 1999 304(a) recommendation. The Tribe did not provide any scientific rationale to show that using the equations as un-ionized ammonia is protective of aquatic life uses.

(2) The ammonia value in the table was changed to µg/L, however, using the equations in footnotes f and g will provide a result mg/L. However, this is not stated anywhere in either footnote f or g, so there is no indication that the result of the equations in f and g must be multiplied by 1,000 in order to get a final result in µg/L. Therefore, simply changing the value in Table 1 did not address the error the Tribe was trying to correct.

The equation for the chronic criterion in µg/L would be:

$$\left(\left(\frac{0.0577}{1+10^{7.688-pH}}+\frac{2.487}{1+10^{pH-7.688}}\right)X\left(\text{MIN }(2.85, 1.45 \text{ X } 10^{0.026 \text{ X } (250-T)})\right)\right) \text{ X } 1000$$

The equation for the acute criterion in µg/L would be:

$$\left(\frac{0.275}{1+10^{7.204-pH}}+\frac{39}{1+10^{pH-7.204}}\right) \text{ X } 1000$$

(3) The chronic ammonia value in Table 1 is in error and the chronic criterion should be 4.15 mg/L (or 4150 µg/L). The Tribe used the incorrect equation when trying to develop the criterion value.

Furthermore on August 22, 2013 EPA published its revised recommended water quality criteria for ammonia. The acute and chronic criteria are more stringent than the 1999 304(a) recommended criteria due to the new toxicity data for freshwater molluscs that are very sensitive to ammonia.

In developing recommendations under § 304(a) of the CWA, EPA bases its criteria on approximately the 5th percentile genera for a given pollutant, which is often the four or five most sensitive genera.[30] Based on the toxicity data, the most sensitive genera used to develop the new acute criterion recommendation are freshwater molluscs. This stands in contrast to the 1999 304(a) recommendation where, in the absence of the more recent mollusc data, the most sensitive genera used to develop the acute criterion were fish, which now appear to be less sensitive to ammonia than freshwater molluscs.

Similarly, based on the available acquired chronic toxicity data, three of the four most sensitive genera used to develop the 2013 recommended chronic criterion were freshwater molluscs. This stands in contrast to the 1999 304(a) recommendation, where only one of the four most sensitive genera used to develop the chronic criterion was a mollusc. The most important difference between the calculation of the 2013 recommendations for chronic criteria and the 1999 304(a) recommendation is the more recent

[30] As per EPA's *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection Of Aquatic Organisms and Their Uses* (PB85-227049, 1985), whenever there are 59 or greater GMAVs in the acute criteria dataset, the FAV is calculated using the four GMAVs which have cumulative probabilities closest to 0.05. In the draft 2009 update of the acute water quality criteria for ammonia, the four GMAVs with cumulative probabilities closest to 0.05 are sensitivity rank 2-5. If there are fewer than 59 GMAVs, the four lowest GMAVs are used to calculate the FAV regardless of cumulative probabilities.

data for molluscs, particularly freshwater mussels which appear to be more sensitive to ammonia than fish (*Draft 2009 Update Aquatic Life Ambient Water Quality Criteria for Ammonia – Freshwater,* December 2009).

Freshwater mussels are widely distributed throughout Washington State (*Freshwater Mussels of the Pacific Northwest*, Ethan Nedeau, Allan K. Smith, Jen Stone, U.S. Fish and Wildlife Service), and each of the Tribe's Class Uses (i.e., Class AA, Class A, and Lake Class) specifically protect molluscs and Class AA waters also protect mussels. Given the wide distribution of freshwater mussels in Washington State, the Tribe's protection of molluscs (and mussels), and toxicity data showing that freshwater mulloscs are particularly sensitive to ammonia, there is not a sound scientific rationale demonstrating that the Tribe's submitted ammonia criteria protect the designated aquatic life uses. Therefore the criteria are inconsistent with CWA § 303(c) and 40 CFR § 131.11.

Remedies to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt ammonia criteria that are based on a sound scientific rationale and protect the Tribe's designated aquatic life uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- Revise the ammonia criteria to be consistent with EPA's *Aquatic Life Ambient Water Quality Criteria for Ammonia – Freshwater, 2013* (EPA 822-R-13-001).

- Revise the ammonia criteria to ensure protection of the Tribe's designated aquatic life uses. Also supply a sound scientific rationale to explain why the alternative ammonia criteria are protective of the Tribe's designated aquatic life uses, taking into account any data on freshwater molluscs.

Freshwater Acute and Chronic Ammonia Aquatic Life Criteria Currently in Effect
Until EPA approves or promulgates numeric acute and chronic aquatic life criteria for ammonia, the previously approved acute and chronic aquatic life criteria are in effect for CWA purposes. The criteria are expressed as total ammonia (as mg N/L):

$$\text{CMC (mg/L)} = \left(\frac{0.275}{1+10^{7.204-pH}} + \frac{39}{1+10^{pH-7.204}}\right)$$

$$\text{CCC (mg/L)} = \left(\frac{0.0577}{1+10^{7.688-pH}} + \frac{2.487}{1+10^{pH-7.688}}\right) \text{X MIN } (2.85, 1.45\ 10^{0.026\ \text{X}\ [25\ -\ T]})$$

B. EPA Action on Freshwater Chronic Aquatic Life Criteria for Iron

In their 2010 water quality standards adoption, the Tribe removed the chronic aquatic life criterion for iron of 1.00 E+03 µg/L, which was originally adopted in its 2003 water quality standards.

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's removal of the freshwater chronic aquatic life criterion for iron.

EPA Rationale
The chronic aquatic life criterion of 1.00E+03 µg/L is the most recent 304(a) recommendation. The Tribe has not provided a scientific justification to show that the aquatic life uses on the Reservation will

be protected in the absence of an iron criterion. EPA has determined that the removal of the chronic aquatic life criterion for iron is inconsistent with CWA § 303(c) and 40 CFR § 131.11.

Remedies to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt a freshwater chronic aquatic life iron criterion that is based on a sound scientific rationale and protects the Tribe's designated aquatic life uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- Adopt iron criterion to be consistent with EPA's 304(a) criterion (i.e., 1000 µg/L).

- Provide a sound scientific rationale to explain why removing the chronic criterion for iron is protective of the Tribe's designated aquatic life uses.

Freshwater Chronic Aquatic Life Iron Criterion Currently In Effect
Until EPA approves or promulgates a numeric chronic aquatic life criterion for iron, the previously approved aquatic life chronic criterion for iron is in effect for CWA purposes. The chronic criterion is 1.00E+03 µg/L.

C. EPA Action on Freshwater Acute and Chronic Aquatic Life Criteria for Pentachlorophenol

In the 2010 water quality standards adoption, the Tribe changed the values for pentachlorophenol in Section 6, Table 1 but retained the same equations in footnote n. Specifically, the following changes were made (new language is underlined):

Compound	*Carcinogen?*	*Acute (a) Criteria*	*Chronic (b) Criteria*	*Water & Organisms*	*Organisms Only*
Pentachlorophenol (n)	*y*	*9.1E+00*	*5.7E+00*	-----	-----

The 2003 water quality standards contained the following values for pentachlorophenol in Section 6, Table 1:

Compound	*Carcinogen?*	*Acute (a) Criteria*	*Chronic (b) Criteria*	*Water & Organisms*	*Organisms Only*
Pentachlorophenol (n)	*y*	*2.03E+01*	*1.28E+01*	-----	-----

Footnote n was referenced and it provides the equations used to develop the pentachlorophenol values indicated in the table above (footnote n also states that the values were derived using a pH value of 7.8).

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revisions to the freshwater acute and chronic aquatic life values for pentachlorophenol contained in Section 6, Table 1.

EPA Rationale
EPA is disapproving the values adopted in Section 6, Table 1 because they do not provide the correct value in accordance with the associated equations found in footnote n, and it is not clear which criteria are the correct, applicable values (i.e., the values in Table 1 or the values resulting from the equations in footnote n).

Remedy to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt the appropriate values into Section 6, Table 1 based on the equations found in footnote n (i.e., acute criterion is 2.03E+01 and the chronic criterion is 12.8E+01).

D. EPA Action on Freshwater Chronic Aquatic Life Criteria for Tributyltin

In the 2010 water quality standards adoption, the Tribe changed the chronic aquatic life criteria for tributyltin from 0.063 µg/L to 0.63 µg/L (6.3E-01) in Section 6, Table 1.

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revisions to the freshwater chronic aquatic life values for tributyltin contained in Section 6, Table 1.

EPA Rationale
The chronic aquatic life criterion of 0.072 µg/L is the most recent 304(a) recommendation. The Tribe has not provided a scientific justification to show that the aquatic life uses on the Reservation will be protected with the revised tributyltin criterion. EPA has determined that the revised chronic aquatic life criterion for tributyltin is inconsistent with CWA § 303(c) and 40 CFR § 131.11.

Remedies to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt a chronic tributyltin criterion that is based on a sound scientific rationale and protects the Tribe's designated aquatic life uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- Adopt a chronic criterion to be consistent with EPA's 304(a) criterion (i.e., 0.072 µg/L).

- Provide a sound scientific rationale to explain why the chronic criterion for tributyltin is protective of the Tribe's designated aquatic life uses.

Freshwater Chronic Aquatic Life Tributyltin Criterion Currently In Effect
Until EPA approves or promulgates a numeric chronic aquatic life criterion for tributyltin the previously approved aquatic life chronic criterion is in effect for CWA purposes. The chronic criterion is 0.063 µg/L.

E. EPA Action on Minor Revisions to Aquatic Life Criteria

In the 2010 water quality standards adoption, the Tribe rounded the following aquatic life criteria to two significant figures:
Lead (acute and chronic)
Nickel (acute)
Silver (acute)
Zinc (acute and chronic)

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the Tribe's revisions to the freshwater aquatic life criteria contained in Section 6, Table 1 and as listed above.

EPA Rationale
The Tribes changes are consistent with EPA recommendation to round criteria to two significant figures (86 FR 22236).

VII. TEMPERATURE CRITERIA IN SECTION 9

A. EPA's Action On Revised Temperature Criteria for Class AA Waters

The following presents the new language contained in Section 9 Paragraph 1(c)(iv), of the WQS. Deleted text indicates text that was removed and new text is underlined and indicates the language that was added by the 2010 water quality standards adoption.

> *(iv) ~~Water used for spawning or rearing by naturalized populations of indigenous salmon or trout. Not to exceed a 7-day average of the daily maximum temperature values greater than 16.5 C from June 1 to September 1. Not to exceed a 7-day average of the daily maximum temperature values greater than 13.5 C between September 1 and October 1 and between April 1 and June 1, and not to exceed 11 C from October 1 to April 1; with no single daily maximum temperature exceeding 18.5 C. Exception for Non-Anadromous Rainbow and Redband Trout. In waters where the only salmonid present is non-anadromous form of naturalized rainbow or redband trout. Temperatures from June 1 to September 1 may be allowed to reach a 7-day average of the daily maximum temperatures of 18.5 C.~~ Temperatures from June 1 to September 1 may be allowed to reach a 7-day average of the daily maximum (7-DADM) temperatures of 16.5 C. Temperature shall not exceed the 7-DADM Table 5 value from September 1st through September 30th as well as from April 1st through May 31st. The 7-DADM temperature shall not exceed 11°C between October 1st and March 31st.*

Table 5, which is referenced in the above provision is found in Section 9 and is provided below:

Table 5. Temperature Standards (degree C).

Date	Class AA 16.5 Standard	Class A 18.5 Standard
01-Apr	11.09	11.12
02-Apr	11.18	11.25
03-Apr	11.27	11.37
04-Apr	11.36	11.49
05-Apr	11.45	11.61
06-Apr	11.54	11.74
07-Apr	11.63	11.86
08-Apr	11.72	11.98
09-Apr	11.81	12.11
10-Apr	11.90	12.23
11-Apr	11.99	12.35
12-Apr	12.08	12.47
13-Apr	12.17	12.60
14-Apr	12.26	12.72
15-Apr	12.35	12.84
16-Apr	12.44	12.97
17-Apr	12.53	13.09
18-Apr	12.62	13.21
19-Apr	12.71	13.34
20-Apr	12.80	13.46
21-Apr	12.89	13.58
22-Apr	12.98	13.70
23-Apr	13.07	13.83
24-Apr	13.16	13.95
25-Apr	13.25	14.07
26-Apr	13.34	14.20
27-Apr	13.43	14.32
28-Apr	13.52	14.44
29-Apr	13.61	14.56
30-Apr	13.70	14.69
01-May	13.80	14.81
02-May	13.89	14.93
03-May	13.98	15.06
04-May	14.07	15.18
05-May	14.16	15.30
06-May	14.25	15.43
07-May	14.34	15.55
08-May	14.43	15.67
09-May	14.52	15.80
10-May	14.61	15.92
11-May	14.70	16.04
12-May	14.79	16.16
13-May	14.88	16.29
14-May	14.97	16.41
15-May	15.06	16.53
16-May	15.15	16.66
17-May	15.24	16.78
18-May	15.33	16.90

Date	Class AA 16.5 Standard	Class A 18.5 Standard
01-Sep	16.32	18.25
02-Sep	16.13	18.00
03-Sep	15.95	17.75
04-Sep	15.77	17.50
05-Sep	15.58	17.25
06-Sep	15.40	17.00
07-Sep	15.22	16.75
08-Sep	15.03	16.50
09-Sep	14.85	16.25
10-Sep	14.67	16.00
11-Sep	14.48	15.75
12-Sep	14.30	15.50
13-Sep	14.12	15.25
14-Sep	13.93	15.00
15-Sep	13.75	14.75
16-Sep	13.57	14.50
17-Sep	13.38	14.25
18-Sep	13.20	14.00
19-Sep	13.02	13.75
20-Sep	12.83	13.50
21-Sep	12.65	13.25
22-Sep	12.47	13.00
23-Sep	12.28	12.75
24-Sep	12.10	12.50
25-Sep	11.92	12.25
26-Sep	11.73	12.00
27-Sep	11.55	11.75
28-Sep	11.37	11.50
29-Sep	11.18	11.25
30-Sep	11.00	11.00

19-May	15.42	17.02
20-May	15.51	17.15
21-May	15.60	17.27
22-May	15.69	17.39
23-May	15.78	17.52
24-May	15.87	17.64
25-May	15.96	17.76
26-May	16.05	17.89
27-May	16.14	18.01
28-May	16.23	18.13
29-May	16.32	18.25
30-May	16.41	18.38
31-May	16.50	18.50

EPA Action

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA is approving part of the revised language and disapproving part of the revised language. Specifically EPA approves the revised language in the first and last sentence in Paragraph 1(c)(iv) as a non-substantive change. This language is as follows:

> *Temperatures from June 1 to September 1 may be allowed to reach a 7-day average of the daily maximum (7-DADM) temperatures of 16.5 C…… The 7-DADM temperature shall not exceed 11°C between October 1st and March 31st.*

The language above is an editorial change that does not change the temperature criteria in effect between June 1 to September 1, and October 1 to March 31 that EPA previously approved in 2003.

EPA disapproves the revisions to the temperature criteria from September 1st to September 30th and from April 1st to May 31st. Specifically, EPA disapproves the revised language in the second sentence in Paragraph 1(c)(iv), which states:

> *…Temperature shall not exceed the 7-DADM Table 5 value from September 1st through September 30th as well as from April 1st through May 31st…*

EPA is also disapproving the Class AA temperature criteria in Table 5.

EPA Rationale

The Tribal water quality standards include the following aquatic life uses in their Class AA waters:

Fish and Shellfish, including:
- Salmonid migration, rearing, spawning, and harvesting.
- Other fish migration rearing, spawning, and harvesting.
- Clam and mussel rearing and, spawning, and harvesting.
- Mollusks, crustaceans and other shellfish rearing, spawning and harvesting.
- The table below summarizes the revisions made to the 2003 WQS:

The table below summarizes the revisions made to the 2003 WQS:

2003 Water Quality Standards		2010 Water Quality Standards	
Time Period	***Criteria***	***Time Period***	***Criteria***
September 1 – October 1	13.5 °C	**September 1 – September 30[1]**	16.32 °C – 11 °C
October 1 – April 1	11.0 °C	**October 1 – March 31**	11.0 °C
April 1 – June 1	13.5 °C	**April 1 – May 31[2]**	11.09 °C – 16.5 °C
June 1 – September 1 **June 1- September 1** (when only non-anadromous form of naturalized rainbow or redband trout are present)	16.5 °C 18.5 °C	**June 1 – August 31** **N/A**	16.5 °C **N/A**
No single daily maximum temperature may exceed	18.5 °C	**No single daily maximum temperature may exceed**	N/A
Footnotes: 1. Temperature criterion decreases incrementally each day (i.e., Sept 1 is 16.32, Sept 2 is 16.13, etc). 2. Temperature criterion increases incrementally each day (April 1 is 11.09°C, April 2 is 11.18 °C, April 3 is 11.27°C, etc).			

EPA relied on the temperature guidance document titled *EPA Region 10 Guidance for Pacific Northwest State and Tribal Temperature Water Quality Standards* (April 2003, hereafter referred to as the Temperature Guidance) to review the Tribe's revisions to its temperature criteria. The Temperature Guidance contains recommended temperature criteria for different salmonid uses (these uses and associated criteria are summarized in the table below), and it also contains a recommended approach for applying the different salmonid uses based on actual fish use information in streams. The scientific rationale and basis for EPA's recommended criteria is described in the Temperature Guidance and the supporting Technical Issue Papers. For more detail on the derivation of the numbers in the tables, see the Temperature Guidance and the Technical Issue Papers. The Temperature Guidance recommends the following temperatures for protecting specific salmonid uses:

SALMONID USES AND CRITERIA	
Salmonid Uses During the Summer Maximum Conditions	Criteria
Salmon/Trout "Core" Juvenile Rearing (Salmon adult holding prior to spawning, and adult and subadult bull trout foraging and migration may also be included in this use category)	16 °C
Salmon/Trout Migration plus "Non-core" Juvenile Rearing	18 °C
Salmon/Trout Migration	20 °C
Salmonid Uses Where/When Occur	
Salmon/Trout Spawning, Egg Incubation, and Fry Emergence	13 °C
NOTES: 1. The temperature metric for each criterion is the 7-DADM. 2. "Salmon" refers to Chinook, Coho, Sockeye, Pink, and Chum salmon. 3. "Trout" refers to Steelhead and coastal cutthroat trout. 4. Bull trout is also known as Char.	

The Tribe has provided no fish information documenting that Class AA waters on the Reservation lack salmon/trout, egg incubation, and fry emergence from September 1 through September 20th (i.e., the time period when the temperature exceeds the 13 °C which is the recommended temperature for spawning, egg incubation and fry emergence); or from April 23 through May 31 (time period when the temperature is greater than the recommended 13 °C). Absent this information there is no way to determine if the revised criteria are protective of the Tribe's designated uses (which include salmonid spawning and rearing) during these time periods. Therefore, EPA is disapproving the revised language

(i.e., *Temperature shall not exceed the 7-DADM Table 5 value from September 1st through September 30th as well as from April 1st through May 31st*), and the associated temperature criteria in Table 5 because it allows the temperature criterion to exceed 13°C during possible spawning, egg incubation, and fry emergence periods

Remedy to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt temperature criteria that are based on a sound scientific rationale and protect designated uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- Revise the temperature criteria consistent with EPA Region 10's Temperature Guidance.

- Resubmit the temperature criteria with a sound scientific rationale to establish that the application of the temperature values is protective of designated uses.

Temperature Criteria Currently in Effect
Until EPA approves or promulgates revised temperature criteria for aquatic life for the time periods September 1 – October 1and April 1- June 1, the previously approved aquatic life temperature criteria are in effect for CWA purposes. The criteria are:

September 1 – October 1:	13.5 °C (7DADM)
April 1- June 1:	13.5 °C (7DADM)

B. EPA Action On Revised Temperature Criteria for Class A Waters

The following presents the new language contained in Section 9 Provision 2(c)(iv) of the WQS. Deleted text indicates text that was removed and new text is underlined and indicates the language that was added in the 2010 water quality standards adoption.

> (iv) ~~*Water used for spawning or rearing by naturalized populations of indigenous salmon or trout. Not to exceed a 7-day average of the daily maximum temperature values greater than 16.5 C from June 1 to September 1. Not to exceed a 7-day average of the daily maximum temperature values greater than 13.5 C between September 1 and October 1 and between April 1 and June 1, and not to exceed 11 C from October 1 to April 1; with no single daily maximum temperature exceeding 18.5 C. Exception for Non-Anadromous Rainbow and Redband Trout. In waters where the only salmonid present is non-anadromous form of naturalized rainbow or redband trout. Temperatures from June 1 to September 1 may be allowed to reach a 7-day average of the daily maximum temperatures of 18.5 C.*~~ *temperatures (sic) from June 1 to August 31 may be allowed to reach a 7-day average (7-DADM) of the daily maximum temperature of 18.5 C. Temperature shall not exceed the 7-DADM Table 5 value from September 1st through September 30th as well as from April 1st through May 31st. The 7-DADM temperature shall not exceed 11°C between October 1st and March 31st.*

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA disapproves the Tribe's revisions to the temperature criteria for Class A waters, and the associated temperature criteria for Class A waters contained in Table 5.

EPA Rationale
The Tribal water quality standards include the following aquatic life uses in their Class A waters:

Fish and Shellfish, including:
- Salmonid migration, rearing, spawning, and harvesting.
- Other fish migration rearing, spawning, and harvesting.
- Mollusks, crustaceans and other shellfish rearing, spawning and harvesting.

The table below summarizes the revisions made to the 2003 WQS:

2003 Water Quality Standards		**2010 Water Quality Standards**	
Time Period	***Criteria***	***Time Period***	***Criteria***
June 1 – September 1	16.5 °C	**June 1 – August 31**	18.5 °C
June 1- September 1 (when only non anadromous form of naturalized rainbow or redband trout are present)	18.5 °C	**N/A**	**N/A**
September 1 – October 1	13.5 °C	**September 1 – September 30**[1]	18.25 °C – 11 °C
April 1 – June 1	13.5 °C	**April 1 – May 31**[2]	11.12 °C – 18.5 °C
October 1 – April 1	11.0 °C	**October 1 – March 31**	11.0 °C
No single daily maximum temperature may exceed	18.5 °C	**No single daily maximum temperature may exceed**	**N/A**
Footnotes: 1. Temperature criterion decrease by 0.25 °C each day (i.e., Sept 1 is 18.25, Sept 2 is 17.75, etc). 2. Temperature criterion increases by approximately 0.12 °C each day (April 1 is 11.12°C, April 2 is 11.25 °C, April 3 is 11.37°C, etc).			

As stated previously, the Temperature Guidance contains recommended temperature criteria for different salmonid uses (these uses and associated criteria are summarized in the "Salmon Uses and Criteria" table above in Section VII.A) and it also contains a recommended approach for applying the different salmonid uses based on actual fish use information in streams.

The Temperature Guidance recommends applying a 16° C temperature criterion for streams that currently have one or more of the following 5 factors:

1. moderate-to-high density summer juvenile salmon rearing
2. summer salmon/steelhead spawning or incubation
3. summer adult/sub-adult bull trout foraging and migration
4. summer juvenile rearing with current streams temperature at or below 16°C
5. the potential to support moderate-to-high density summer juvenile rearing that is important for the recovery of salmonids

The Tribe provided no fish information documenting that Class A waters on the Reservation lack the above referenced factors, or that higher temperatures between April 17th and May 31st, and between September 1st and September 21st, will be protective of the Tribes designated aquatic life uses (which include salmonid spawning and rearing). This temperature revision appears to protect only rainbow and redband trout and does not necessarily provide adequate spring and summer temperatures needed to protect other types of salmonids. Without specific information documenting which types of salmonids reside in Class A waters, it is not possible to determine if the Tribe's designated uses are being protected. Therefore, EPA is disapproving the revisions to Section 9, Paragraph (2)(c)(iv).

Remedy to Address EPA's Disapproval
To address this disapproval, the Tribe must adopt temperature criteria that are based on a sound scientific rationale and protect designated uses. There are several means by which the Tribe may potentially accomplish this objective. They include:

- Revise the temperature criteria consistent with EPA Region 10's Temperature Guidance.

- Resubmit the temperature criteria with a sound scientific rationale to establish that the applications of temperature values are protective of designated uses.

Temperature Criteria Currently in Effect
Until EPA approves or promulgates revised temperature criteria for aquatic life, the previously approved aquatic life temperature criteria are in effect for CWA purposes.

VIII. Surface Waters Classifications

In Section 11 of the Tribe's water quality standards, specific surface waters on the Spokane Reservation are classified. In the 2010 water quality standards adoption, the Tribe included Ente' Creek as a Class A water. Additionally, the Tribe corrected a spelling error. The Tribe corrected the following (new letters that were added in the 2010 WQS adoption are underlined):

Chamokane (Tsh<u>i</u>m<u>i</u>k<u>ai</u>n) Creek.

EPA Action
In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the Tribe's addition of Ente' Creek as a Class A water in Section 11 of the water quality standards. In the 2003 water quality standards, all unclassified streams that were not tributaries to Class AA streams were designated as Class A waters (Section 10); therefore, Ente' Creek was previously classified as a Class A water by default. Ente' Creek is now specifically designated as Class A in Section 11.

Additionally, EPA acknowledges the editorial change to the spelling of *Tshimikain* and approves it as a non-substantive editorial change.

IX. Mixing Zone Provisions

The following presents the new language contained in Section 13 of the WQS. Deleted text indicates text that was removed and new text is underlined and indicates the language that was added in the 2010 water quality standards adoption.

13. IMPLEMENTATION

(1) All discharges from point sources and all activities which generate nonpoint source pollution shall be conducted so as to comply with this chapter.

~~*(2) Activities which cause pollution of storm water shall be conducted so as to comply with these water quality standards.*~~

(2) The standards required in this chapter may not be met by using a mixing zone, except where:

(a) the allowable size, location and duration of the mixing zone and associated effluent limits are established by the Department as part of a cleanup performed under the Federal or Tribal cleanup laws, and as established, the mixing zone will be at least as protective of human health and the environment as a mixing zone established under the laws of the State of Washington; and

(b) the size of the mixing zone and the concentrations of pollutants present shall be minimized; and

(c) overlapping mixing zones shall only be allowed if, in combination, the requirements of subsection (f)(sic) are satisfied; and

(d) water quality criteria shall not be violated outside of the boundary of a mixing zone as a result of the discharge for which the mixing zone was authorized; and

(e) the discharge is either:

(i) at a sufficient depth below the surface of the receiving water body that the criteria applicable to the constituent of concern being addressed by using the mixing zone is met at the water body's surface; or

(ii) located at a distance from the shore that ensures sensitive human and wildlife receptors are not likely exposed at the water body's surface for extended periods.(3) Activities which cause pollution of stormwater shall be conducted so as to comply with these water quality standards.(sic)

EPA Action

In accordance with its CWA authority, 33 U.S.C. § 1313(c)(3) and 40 CFR Part 131, EPA approves the Tribe's mixing zone policy.

EPA Rationale

Mixing zones are areas where instantaneous or rapid and complete mixing of discharges with receiving waters does not occur, and pollutant concentrations are allowed to exceed otherwise applicable water quality criteria. The federal water quality standards regulation at 40 CFR § 131.13 provides that states and tribes have the discretionary authority to include regulatory mixing zone policies in their water quality standards. When mixing zone policies are included, they are subject to EPA review and approval or disapproval pursuant to § 303(c) of the CWA. As explained in EPA's Advanced Notice of Proposed Rule Making, 63 FR 36787, July 7, 1998, EPA interprets the CWA as allowing the use of mixing zones as long as the provisions addressing toxicity at CWA § 101(a)(3) are met and the designated uses of the waterbody as a whole are protected. EPA's allowance of mixing zones is based on a premise that surface water quality criteria can be exceeded under limited circumstances without causing unacceptable toxicity and impairment of a water's uses.

In general, the Spokane Tribe's mixing zone policy does not allow the use of mixing zones with an exception made for effluent limitations that are established as part of a cleanup performed under Federal or Tribal Clean up Laws.[31] The purpose of the Tribal clean up law is to provide remedial law for the cleanup of hazardous substances sites, and to prevent the creation of future hazards due to improper use or disposal of hazardous substances on or into the Reservation Environment. The chapter is consistent with CERCLA.

Since the mixing zone policy is so limited in what it pertains to, is associated with CERCLA clean up sites, and limits the sizing of the mixing zone to be consistent with the State of Washington's requirements, this policy is consistent with the requirements of CWA 40 CFR Part 131.

[31] The WQS define Federal clean up law as the Comprehensive Environmental, Response, Compensation and Liability Act, 42 U.S Sec 9601, *it seq* (more commonly known as Superfund); and it defines "Tribal clean up law as the Hazardous Substances Control Act, Chapter 34, Law and Order Code of the Spokane Tribe of Indians. Tribal clean up laws are consistent with CERCLA.

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 131

[EPA-HQ-OW-2012-0095; FRL-]

RIN 2040-AF33

Response-to-Comments for Water Quality Standards; Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

SUMMARY: On April 5, 2012 the Environmental Protection Agency (EPA) issued a Notice of Proposed Rulemaking to amend the federal regulations to withdraw certain human health and aquatic life water quality criteria applicable to waters of New Jersey, Puerto Rico, and California's San Francisco Bay.

In 1992, EPA promulgated the "National Toxics Rule" ("NTR") to establish numeric water quality criteria for 12 states and two Territories, including New Jersey, Puerto Rico and parts of California. On May 18, 2000, EPA then promulgated a final rule known as the ''California Toxics Rule'' (''CTR'') in order to establish numeric water quality criteria for priority toxic pollutants for the State of California that were not previously in the NTR. These two states and one territory have now adopted, and EPA has approved, water quality criteria for certain pollutants included in the NTR. Since California, New Jersey, and Puerto Rico now have criteria effective under the Clean Water Act, for the same priority toxic pollutants in the NTR, EPA has determined that the federally promulgated criteria are no longer needed for these pollutants. The comments received and the EPA's Response to those comments is listed below.

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Proposed Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

Comment On: EPA-HQ-OW-2012-0095-0001
Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

Document: EPA-HQ-OW-2012-0095-0002
Anonymous public comment

The EPA should not withdraw the federally promulgated water quality criteria for the state of New Jersey because establishing less stringent standards for the listed pollutants is contrary to the purpose and goals of both the CWA and the National Toxics Rule, particularly with regard to protecting human health.

As laid out in 40 CFR 131.2, the National Toxics Rule (codified in 40 CFR 131.36) was promulgated under §303(c)(2)(B) of the CWA for "the dual purposes of establishing the water quality goals for a specific water body and serve as the regulatory basis for the establishment of water-quality-based treatment controls and strategies *beyond the technology-based levels of treatment required* by sections 301(b) and 306 of the Act." (emphasis added).

The phrase "beyond the technology-based levels of treatment" indicates that water quality standards for bodies of water were enacted to improve water quality *in addition to* the effluent limitations of the CWA, so that both strategies could work in tandem. Water quality criteria were not produced to replace effluent limitations, but rather, were necessary to reach the

goals of the CWA which could not be attained simply through effluent limitations due to the difficulty in regulating point sources.

All but one of the pollutants to which New Jersey seeks to apply laxer standards are toxic pollutants, as listed under 40 CFR 401.15. These pollutants are numbered on the list: 22. Copper, 27. Ichloroethylene, 43. Isophrone, 44. Lead, 45. Mercury, 47. Nickel, 59. Tetrachloroethane, and 63. Trichloroethane. The one pollutant not on the toxic list, gamma-BHC (also called Lindane) is still of serious concern as it was dubbed "moderately toxic" by the World Health Organization in 2005.

Looking only at the effluent standards for toxic pollutants clearly shows the will of our Legislature to treat all toxic pollutants with more rigorous standards to carry out the purpose of the CWA: "to restore and maintain the chemical, physical, and biological integrity of the Nation's waters." Toxic pollutants are subject to the most rigorous technology treatment standard for existing sources under the CWA, the "best available technology economically achievable... which will result in reasonable further progress toward the national goal of eliminating the discharge of all pollutants..." §301(b)(2)(A). Since the EPA only is required to *consider* costs in determining the BAT and does not have to carry out a cost-benefit analysis, weighing costs against the benefits of effluent reduction as it does with the BPT and BCT standards, the choice to apply BAT to toxic pollutants confirms Congress's intent to regard them with heightened caution.

Since the CWA unambiguously established its goal of treating toxic pollutants more rigorously than conventional pollutants, any regulation promulgated to explicitly further this interest should be read to require states to impose standards at least as stringent as federal standards. Giving states power to regulate their water bodies is a reasonable goal as far as it

recognizes the familiarity state agencies have with their geographic area and how that can make them more effective in responding to the specific water quality challenges than the EPA. This concept, however, should not translate into an allowance for states to pick and choose which federal regulations they wish to implement, particularly in states like NJ that have a troubled history of compliance.

Given the current problems in NJ's ability to meet water quality criteria for aquatic life, and the fact that NJ exceeds federal phosphorus standards, it is inappropriate to consider lower standards of any kind on water quality. According to the 2010 Integrated Water Quality Report published by the NJDEP, the number of limited use and impaired waterways in the state grew by 9.8% in the past two years. The report also stated that the three largest sources of pollution are non-point, stormwater discharges, and combined sewer overflow. Since all three of these are difficult or impossible to regulate through effluent limitations, it is necessary to maintain stringent quality standards for the surface waters to meet the overall goal of improving water quality nationwide.

Additionally, as the 2010 report suggests, NJ should not be taken off of NTR because it has been sanctioned in the past for not expanding their water quality monitoring network, indicating that the state is not yet ready to take on the full responsibility of regulating its waters.

Furthermore, NJ's proposed changes could lead to harmful conditions in the Delaware and Chesapeake bay as water body specific criteria ignores that water moves between water bodies and ultimately ends up in bays that provide water to other states. In this sense, allowing NJ an exemption to the strict federal standards would be inequitable as it could negatively impact other states that are held to higher standards.

> "The [NJDEP's] goal is for all waters to fully support <u>all</u> uses, except for fish consumption. Non-support of the fish consumption use is caused by unsafe

> levels of toxic contaminants in fish tissues, which is generally due to legacy pollutants (like PCBs) or air deposition (like mercury), rather than active point source discharges. These types of pollutants generally require national or regional approaches to restore water quality. In New Jersey, non-support of the fish consumption use is addressed through public health advisories rather than pollution control measures." (http://www.state.nj.us/dep/wms/bwqsa/generalinfo.htm)

It is imperative that the standards for the toxic pollutants listed by the NJDEP remain subject to the more protective federal standards. Consideration of just two of the pollutants, lead and copper, illustrates this point:

Lead is "a highly toxic metal the agency considers a major public health threat.", according to the EPA. The national Centers for Disease Control considers lead to be the country's number one preventable pediatric health problem. More than 30 Million Americans are drinking water with lead levels in excess of the Maximum Contaminant Level set by the EPA. (http://www.pure-earth.com/lead.html)

The "Action Level" (concentration which, if exceeded, triggers treatment) for copper has also been set at 1.3 ppm because EPA believes, given present technology and resources, this is the lowest level to which water systems can reasonably be required to control this contaminant should it occur in drinking water at their customers home taps. EPA has found copper to potentially cause the following health effects when people are exposed to it at levels above the Action Level. (http://www.freedrinkingwater.com/water-contamination/copper-contaminants-removal-water.htm)

In order to further the goals of both the CWA and the NJDEP, NJ should remain subject to the NTR, and be required to adopt standards at least as stringent as the federal ones.

EPA Response:

EPA appreciates the comments and to the extent a response is necessary, within the scope of this final rule, are addressed below.

The Clean Water Act tasks the States, Territories and authorized Tribes with adopting designated uses for their surface waters, and in adopting criteria to protect those uses. Federal criteria are being withdrawn for New Jersey where the state has adopted, and EPA has approved criteria that, while not as stringent as the promulgated criteria, are scientifically defensible, protective of the designated uses and consistent with the Clean Water Act and EPA's implementing regulations at 40 CFR 131.11.

The following is the list of pollutants (12 criteria) for which New Jersey adopted criteria, and which EPA approved, that are less stringent than the promulgated federal criteria, but that nonetheless meet the requirements of the CWA and EPA's implementing regulations at 40 CFR 131.11 covered in this proposal:

• Copper (aquatic life—marine (acute and chronic)).
• Lead (aquatic life—freshwater (chronic) and marine water (chronic)).
• Mercury (aquatic life—freshwater (chronic) and marine water (chronic)).
• Nickel (aquatic life—marine water (chronic)).
• 1,1–Dichloroethylene (human health—organisms only).
• 1,1,2,2–Tetrachloroethane (human health—organisms only).
• 1,1,2–Trichloroethane (human health—organisms only).
• Isophrone (human health— organisms only).
• gamma-BHC (human health—organisms only).

The following six New Jersey criteria are less stringent than the NTR because they are equal to EPA's most recent 304(a) criteria recommendations:

- Copper (aquatic life – marine (acute and chronic))
- Mercury (aquatic life – freshwater (chronic) and marine water (chronic))
- Isophrone (human health – organisms only)
- gamma-BHC (human health – organisms only)

The following three New Jersey criteria are less stringent than the NTR because New Jersey developed applicable criteria as outlined below:

- Lead (aquatic life – freshwater (chronic) and marine water (chronic)): New Jersey updated its aquatic freshwater criteria for lead as nonhardness-dependent criteria. In addition, the State used conversion factors recalculated by the Delaware River Basin Commission for both fresh and marine criteria, which are more stringent than the nationally recommended conversion factors, as well as the national species list and updated toxicity data reviewed and accepted by EPA (Great Lakes Water Quality Initiative, 1991).

- Nickel (aquatic life – marine water (chronic)): New Jersey adopted saltwater criteria for nickel which were recalculated based upon the most recent peer reviewed saltwater toxicity data available.

The following three New Jersey criteria are less stringent than the NTR because New Jersey developed applicable criteria following the scientific methodology recommended by EPA, but used toxicity factors recommended by the New Jersey Drinking Water Quality Institute (NJDWQI) rather than the toxicity factors available in IRIS to ensure consistency with the State's Safe Drinking Water Program

- 1,1-Dichloroethylene (human health – organisms only)
- 1,1,2,2-Tetrachloroethane (human health – organisms only)
- 1,1,2-Trichloroethane (human health – organisms only)

In summary the above-referenced criteria have all been found to be scientifically defensible, protective of the designated uses, and consistent with the Clean Water Act and EPA's implementing regulations at 40 CFR 131.11.

In terms of the specific concerns raised by the commenter, EPA offers the following:

- In terms of the development of water quality based effluent limitations (WQBELs) for point source discharges, where such limits are found to be required the resultant criteria are used by States to derive these WQBELs in order to protect designated uses.

- The withdrawal of the federal criteria is not intended to impact the scope of the State's water quality monitoring network.

- With regard to the protection of Delaware and Chesapeake Bay, New Jersey remains obligated to comply with the requirements of 40 CFR 131.10(b) which states that, "in designating uses of a water body and the appropriate criteria for those uses, the State shall take into consideration the water quality standards of downstream waters and shall ensure that its water quality standards provide for the attainment and maintenance of the water quality standards of downstream waters."

- Finally, with regard to the protection of drinking water, States adopt different sets of water quality criteria for the protection of aquatic life or human health. One of the purposes of this rule is to withdraw the federal aquatic life criteria, not human health criteria, for chronic and acute copper and lead, for fresh and marine waters designated for aquatic life use. The removal of the federal aquatic life criteria will allow New Jersey to implement its adopted and EPA-approved aquatic life criteria for copper and lead, and will not impact any drinking water-based criteria that are already adopted by the State. Therefore, the level of protection currently provided by the State for drinking water will not change with this rulemaking.

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Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

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Anonymous public comment

Submitter Information

Government Agency Type: Federal

General Comment

HELP ! Our water which falls from the sky onto our neighborhoods, fields and mountains, runs down our gutters and creeks, swells our rivers and cleans and maintains the Sacramento Delta is being 'sold' by folks I don't remember electing ! I know those folks and corporations in southern California need some of our water but they are killing the Delta, an area that supports vast amounts of 'Aquatic nurseries'. If this was happening in Brazil, ecologist from Davis to 'Frisco would be screaming and signing petitions about how 'We Must Save....', But..because its in our back yard, We say / do nothing.
As a remedy I suggest we triple the price of our water being shipped via the massive salmon killing pumps. When water is expensive to the mega corporations they will find a more sustainable means to farm the desert! I personally am willing to pay 25 cents more per melon for wanting my grand kids see a delta I saw when I was young.

EPA Response:

EPA thanks you for your interest in water issues concerning the San Francisco Delta. Your comment concerns water quantity (water flow) issues in the Delta, while our proposed rule concerns water quality in the Bay, specifically, the aquatic life saltwater cyanide criteria in San Francisco Bay. EPA is only taking comment on the water quality criteria for cyanide in San

Francisco Bay at this time. However, we appreciate your interest in the Delta, and hope you continue to express your thoughts and concerns on these important matters.

PUBLIC SUBMISSION

As of: December 04, 2012
Received: May 21, 2012
Status: Posted
Posted: May 22, 2012
Tracking No. 81018a68
Comments Due: June 04, 2012
Submission Type: E-mail

Docket: EPA-HQ-OW-2012-0095
Proposed Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

Comment On: EPA-HQ-OW-2012-0095-0001
Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

Document: EPA-HQ-OW-2012-0095-0028
Comment submitted by Naomi Feger, Division Chief, San Francisco Bay Regional Water Quality Control Board

---

Submitter Information

Submitter's Representative: Barbara Baginska
Organization: San Francisco Bay Water Board
Government Agency Type: State

General Comment

See attached file(s)

Attachments

Cover Letter

Comment

May 17, 2012
CWIQs Place no. 718825
U.S. Environmental Protection Agency, Region 9
75 Hawthorne Street, WTR-3
San Francisco, California 94105
Sent via email to ow-docket@epa.gov
Sent via email to Diane Fleck: fleck.diane@epa.gov
Subject: PROPOSED WITHDRAWAL OF CERTAIN FEDERAL WATER QUALITY CRITERIA APPLICABLE TO CALIFORNIA, NEW JERSEY AND PUERTO RICO
Docket No. EPA-HQ-OW-2012-0095
Dear Ms. Fleck:

Please accept these comments into the docket for the withdrawal of the federally promulgated saltwater aquatic life cyanide criteria for San Francisco Bay, as referenced above.

The San Francisco Bay Regional Water Quality Control Board (Water Board) is the State of California's regional office with responsibility for enhancing and maintaining the water quality of the San Francisco Estuary. The San Francisco Bay Water Quality Control Plan establishes applicable water quality standards, including beneficial uses and water quality objectives, to protect water quality in the Estuary. The Water Board strives to implement water quality standards that are most relevant and protective of beneficial uses in the Bay.
We fully support the EPA action to amend the federal regulations to withdraw promulgated federal water quality criteria for cyanide applicable to San Francisco Bay and the EPA's approval of the site-specific aquatic life objectives put forward by the Water Board.

In December 2006, the Water Board adopted Resolution (R2-2006-0086) to establish site-specific marine cyanide objectives (acute 9.4 μg/L and chronic 2.9 μg/L) for all segments of San Francisco Bay to replace the existing National Toxics Rule (NTR) acute and chronic objectives of 1 μg/L. The adopted site-specific objectives reflect the relevant aquatic organisms present in the Bay and follow both state and federal guidance and policy guiding development of site-specific objectives. The state Policy for Implementation of Toxics Standards for Inland Surface Waters, Enclosed Bays, and Estuaries of California allows for consideration of site-specific objectives when permit limits based on existing water quality objectives may not be attainable, the current objectives are not appropriate for the water body, and there is no evidence of adverse water quality impacts. All these conditions are met for cyanide in San Francisco Bay. In particular, the NTR water quality criteria are heavily influenced by toxicological data for one species that is not present in San Francisco Bay, and are therefore not fully applicable. Despite the fact that the site-specific objectives are less stringent than the NTR criteria, cyanide data collected in the Bay consistently show concentrations that are well below the NTR objective. Furthermore, cyanide does not persist in natural waters and does not bioaccumulate in biota. We appreciate the opportunity to support the EPA action to update the NTR criteria for cyanide in San Francisco Bay.

If you have any further questions, please contact Barbara Baginska at 510 622-2474, or via e-mail at bbaginska@waterboards.ca.gov.

Sincerely,
Naomi Feger
Division Chief

EPA Response:

EPA appreciates this letter of support from the State of California's San Francisco Bay Regional Water Quality Control Board. We look forward to continuing to work with the Board on water quality issues.

PUBLIC SUBMISSION

As of: December 04, 2012
Received: June 04, 2012
Status: Posted
Posted: June 05, 2012
Tracking No. 81031243
Comments Due: June 04, 2012
Submission Type: Web

Docket: EPA-HQ-OW-2012-0095
Proposed Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

Comment On: EPA-HQ-OW-2012-0095-0001
Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

Document: EPA-HQ-OW-2012-0095-0029
Comment submitted by Jill Lipoti, Director, Water Monitoring and Standards, New Jersey Department of Environmental Protection (NJDEP)

Submitter Information

Submitter's Representative: Jill Lipoti, Director of Water Monitoring and Standards
Organization: Water Monitoring and Standards, New Jersey Department of Environmental Protection (NJDEP)
Government Agency Type: State
Government Agency: Water Monitoring and Standards, New Jersey Department of Environmental Protection (NJDEP)

General Comment

See attached file(s)

Attachments

Comment

June 4, 2012
U.S. Environmental Protection Agency
Mail Code: 28221 T
Water Docket
1200 Pennsylvania Ave., NW
Washington, DC 20460
PO Box 420 (Mail Code 401-041)
401 East State Street
Trenton, New Jersey 08625-0420
Telephone: 609-292-1623
Fax: 609-633-1276
http://www.nj.gov/dep/wms/
Attn: Docket ID No. EPA- HQ-OW-2012-0095
Via email to: OW-Docket@epa.gov
Re: Docket ID No. EPA-HQ-OW-2012-0095
Proposed Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico

The New Jersey Department of Environmental Protection (NJDEP) appreciates the opportunity to comment on the U.S. Environmental Protection Agency's (USEPA), Proposed Withdrawal of Certain Federal Water Quality Criteria Applicable to California, New Jersey and Puerto Rico (Proposed Withdrawal) (66 FR 20585, April 5, 2012). NJDEP is pleased with USEPA's action to withdraw National Toxics Rule (NTR) aquatic life and human health water quality criteria applicable to New Jersey. NJDEP adopted criteria for those pollutants under the NTR through several revisions to the New Jersey Surface Water Quality Standards (N.J.A.C. 7:9B) since 1992. These criteria were approved by the USEP A subsequent to each revision.

USEPA has identified nine pollutants (12 criteria), which New Jersey adopted and USEPA approved, that are less stringent than the Federal promulgated NTR criteria. USEPA has compared NJDEP's current surface water quality criteria with the 1992 NTR criteria to arrive at the conclusion that these criteria are less stringent. However, USEPA has updated several of their criteria since 1992. When compared with the current USEPA National Recommended Water Quality Criteria http://water.epa.gov/scitech/swguidance/standards/current/index.cfm), only six criteria are less stringent than USEPA's current recommended criteria. The following are comments on the criteria that are less stringent than current USEP A current recommendations.

Lead:
NJDEP has updated aquatic freshwater criteria for Lead in 2002 (34 N.J.R. 537(a); January 22, 2002), as a non-hardness-dependent criteria. In addition, NJDEP used conversion factors recalculated by the Delaware River Basin Commission (DRBC) for both fresh and marine criteria. USEPA approved these criteria on August 16, 2002 and indicated that they are in the

process of updating criteria for lead. NJDEP may review its aquatic criteria for lead when USEPA updates its recommendations to determine if NJDEP criteria are still protective using the most recent scientific data.

Nickel:
NJDEP has updated aquatic marine criteria for update in 2006 (38 N.J.R. 4449(a); October 16, 2006) based on newer scientific information because USEPA failed to include its criteria recommendations based on new information. Marine criteria were recalculated using Technical Information Related to Developing a Saltwater Nickel Addendum to the Ambient Water Quality Criteria Document, 2003 (http://www.state.nj .us/dep/wms/bwqsa/support_ docs.htm).
USEPA approved these criteria on December 20, 2006. On April 6, 2010, USEPA, through a letter to Ronald Popowski, USFWS, indicated these criteria are more scientifically-sound and are not likely to adversely affect any applicable federally-listed aquatic or aquatic-dependent species under USFWS jurisdiction.

1,1,2,2-Tetrachloroethane, 1,1,2-Trichloroethane, and 1,1-Dichloroethylene:
NJDEP has updated human health criteria for saline water based upon fish only exposure for 1,1 ,2,2-Tetrachloroethane, 1,1,2- Trichloroethane, and 1,1 - Dichloroethylene in 2006 (38 N.J.R. 4449(a); October 16, 2006).
NJDEP developed these criteria following the scientific methodology recommended by USEPA. However, the NJDEP used toxicity factors recommended by the New Jersey Drinking Water Quality Institute (NJDWQI) rather than the toxicity factors available in IRIS to ensure consistency with our Safe Drinking Water Program. USEPA approved these criteria on December 20, 2006.

As part of the 2009 NJDWQI review, 1,1 ,2,2-Tetrachloroethane, 1,1 ,2-Trichloroethane, and 1, 1-Dichloroethylene, were classified as Suggestive Carcinogens (Possible Human Carcinogens). NJDWQI has reviewed the health effects information and has recommended revisions to these health based criteria. NJDWQI recommendations are: the human health criteria in saline waters for 1,1 ,2,2-Tetrachloroethane should be 14)µg/L which is equal to the current USEPA recommendation; the human health marine criteria for 1,1,2- Trichloroethane should be 14)µg/L which will be more stringent than the current US EPA recommendation of 16 µg/L; and the human health marine criteria for 1,1 -Dichloroethylene should be 1,286 µg/L which will be more stringent than the current US EPA recommendation of 1700 µg/L. In accordance with N.J.A.C. 7:9B-1.5(c) 6, once the Maximum Contaminant Levels (MCL)'s for these criteria are revised in the Safe Drinking Water Act Rules, the Department will publish a notice of administrative change in the New Jersey Register to update these criteria in the Surface Water Quality Standards.

I hope that the above comments on the Proposed Withdrawal will assist you in finalizing the document. Feel free to contact Debra Hammond by email at Debra.hammond@dep.state.nj .us or by phone at 609-777-1753 if you have any questions.

Sincerely
Jill Lipoti, Director, Water Monitoring and Standards
NJ Department of Environmental Protection

P.O. Box 420 (Mail Code 401-041)
401 East State Street
Trenton, NJ 08625-0420

EPA Response:

EPA appreciates this letter of support from the State of New Jersey's Department of Environmental Protection (NJDEP). We look forward to continuing to work with the NJDEP on water quality issues.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 10
1200 Sixth Avenue, Suite 900
Seattle, WA 98101-3140

OFFICE OF
WATER AND WATERSHEDS

January 20, 2015

Don Essig
Idaho Department of Environmental Quality
1410 N. Hilton
Boise, Idaho 83706

RE: EPA comments on Idaho's Discussion Paper #7 Risk Management and Protection of Human Health

Dear Don:

EPA appreciates the opportunity to provide comments to the Idaho Department of Environmental Quality (DEQ) on the discussion paper, Risk Management and Protection of Human Health, which DEQ presented at the December 3, 2014 negotiated rulemaking meeting. The EPA is very appreciative of the challenging work that DEQ has undertaken thus far in consideration of revising its human health water quality criteria, which has included a robust public process and review of the factors used to derive human health criteria.

In general, EPA found DEQ's discussion paper to be well written. However, EPA has concerns about some of the statements included in the paper and the absence of discussion on some important issues. While we are providing more specific comments below, the EPA is available and interested in continuing discussions with DEQ about risk management considerations in the rulemaking process. As you know, EPA also has been very engaged in Washington's human health water quality rule development and has emphasized the importance of having states fully assess potential health risks to higher fish consumers, taking into consideration factors such as environmental justice and tribal treaty rights. These issues were not addressed in DEQ's issue paper and EPA believes it is important for DEQ to fully consider these and other issues noted below as it moves forward in the rulemaking process.

SPECIFIC COMMENTS

1. With regards to characterization of EPA's reference dose (pg. 1), it should be noted that the reference dose is currently based on the most sensitive toxic endpoint exhibited by the most sensitive species. EPA is moving towards a more complete description of all of the dose response relationships associated with exposures to non-carcinogens, not just the effect associated with the current reference dose methodology.

2. The paper cites recent work done by the State of Florida on relative source contribution. EPA is still evaluating their analysis.

3. The citation of the percentages of cancer associated with occupational and environmental causes in the American Cancer Society (ACS) publication (pg. 2) is not well documented in

the ACS publication. However, it appears that the percentages of cancers associated with these causes is from Doll and Peto (1981). If so, it is important to note that Doll and Peto's analysis has a number of weaknesses which are well characterized in the 2008-2009 report on the President's Panel on Cancer, "Reducing Environmental Cancer Risk, What We Can Do Now," http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf. Specifically, it is now recognized that the development of cancer depends on multiple factors and that the contribution of environmental factors is likely underestimated in Doll and Peto's work. Doll and Peto relied primarily on epidemiologic studies of workers in large industries and failed to include minorities, deaths among persons aged 65 and older, exposures in smaller workplaces, and the effects of indirect contact with carcinogens. Even if Doll and Peto's suggested percentages were deemed to be accurate, given the population of the United States, the general probability of getting cancer, and the costs of cancer treatment, occupational and environmental cancer exacts a staggering cost to the U.S., as well as costs in human suffering that are difficult to quantify.

4. Though it is true that EPA generally assumes that there is no dose threshold associated with cancer risk (pg. 2), EPA's 2005 Cancer Guidelines, http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF, clearly acknowledge that carcinogens may have a threshold mechanism of action. Chloroform and formaldehyde are examples of chemicals that utilize cancer risk assessment based on a non-linear mode of action.

5. In its discussion paper, DEQ identifies factors that might be considered in developing acceptable risk levels (pg. 3). DEQ also specifically states (pg. 8), "the concept of ALARA has some significance to the development of water quality criteria," and "the challenge is to develop "reasonably achievable" criteria." To clarify, EPA's standard of review under the Clean Water Act and EPA's implementing regulations at 131.11(a) is that water quality criteria must protect applicable designated uses and be based on sound scientific rationale. In developing 304(a) criteria and reviewing state water quality standards under CWA 303(c), EPA does not consider economic impacts or the technological feasibility of meeting the criteria in ambient water. Therefore, EPA believes the list of factors relevant to development of water quality criteria is narrower than the list presented in the discussion paper.

6. The Idaho paper discusses the origins of the use of one in a million risk (pg. 3). However, the origin is not as relevant as an analysis of the factors considered when selecting a risk level to use for developing risk-based water quality standards (e.g., What is the appropriate risk level associated with criteria for regulating involuntary exposure of U.S. citizens to chemicals in the Nation's waters?). The focus should be on evaluation and discussion of the issues covered in the Idaho paper as informed by the enabling statute, the Clean Water Act, and its implementing regulations not the historical origin of one in a million risk.

7. In considering risk levels used by other regulatory programs (pg. 4), DEQ should define how risk is considered as specified in the enabling statutes and associated implementation regulations. Further considerations include whether or not risk is involuntary (as is the case for exposure to contaminants in environmental media) or is voluntary (as is the case for some occupational exposures). Another consideration is the scope of the program of interest (e.g.

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the limited geographic scope of CERCLA/RCRA cleanups, the national scope of ambient water quality criteria, or regulation of the workplace). A useful addition to the discussion paper would have been a discussion of how other entities have considered risk in setting water quality criteria as opposed to comparing risk levels across programs with varied regulatory objectives and mandates.

8. The discussion paper's section on flexibility in choice of risk level (pg. 7) does not fully describe the recommended risk range for setting AWQC. The language within the paper focuses on use of 10^{-6} to 10^{-5}. However, EPA's Human Health Methodology (EPA 2000) notes that States and Tribes can choose more stringent risk levels, such as 10^{-7}.

9. The discussion of voluntary vs. involuntary risk (pg. 7) touches on the responsibility of government to reduce risks. However, the discussion paper does not address the important issue of environmental justice and how DEQ should consider those issues, recognizing that tribes and other low-income, minority populations have generally been well-documented to have exposures to contaminants in fish and shellfish exceeding those experienced by the general population. These issues, along with tribal trust responsibilities, including treaty rights, are important considerations. The conclusions section (pg. 8) should address these types of issues.

We look forward to continued work with DEQ on this effort and are available if you would like to discuss our comments further. Please contact Lon Kissinger (206-553-2115) or myself (206-553-1834) if you have any questions.

Sincerely,

Lisa Macchio
Water Quality Standards Coordinator

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Subject: FW: EPA Comments on Idaho's Discussion Paper #7 Risk Management
Attachments: EPA Comments to Discussion Paper #7 Risk Management.pdf

From: "Macchio, Lisa" <Macchio.Lisa@epa.gov>
Date: Wednesday, January 21, 2015 2:29 PM
To: Kris Holm <krisholm@comcast.net>
Cc: "Fleisig, Erica" <Fleisig.Erica@epa.gov>, "Chung, Angela" <Chung.Angela@epa.gov>
Subject: FW: EPA Comments on Idaho's Discussion Paper #7 Risk Management

From: Macchio, Lisa
To: Don Essig; Jeffrey.Fromm@deq.idaho.gov
Subject: EPA Comments on Idaho's Discussion Paper #7 Risk Management

Don and Jeff – Please find attached EPA's comments on your most recent discussion paper. Thank you for the opportunity to comment. If you have any questions please feel free to contact Lon or myself.

Lisa Macchio
U.S. EPA, Region 10 (OWW-131)
1200 Sixth Avenue, Suite 900
Seattle, WA 98101
(206) 553-1834
macchio.lisa@epa.gov

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 10
1200 Sixth Avenue, Suite 900
Seattle, WA 98101-3140

OFFICE OF
WATER AND WATERSHEDS

January 20, 2015

Don Essig
Idaho Department of Environmental Quality
1410 N. Hilton
Boise, Idaho 83706

RE: EPA comments on Idaho's Discussion Paper #7 Risk Management and Protection of Human Health

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In general, EPA found DEQ's discussion paper to be well written. However, EPA has concerns about some of the statements included in the paper and the absence of discussion on some important issues. While we are providing more specific comments below, the EPA is available and interested in continuing discussions with DEQ about risk management considerations in the rulemaking process. As you know, EPA also has been very engaged in Washington's human health water quality rule development and has emphasized the importance of having states fully assess potential health risks to higher fish consumers, taking into consideration factors such as environmental justice and tribal treaty rights. These issues were not addressed in DEQ's issue paper and EPA believes it is important for DEQ to fully consider these and other issues noted below as it moves forward in the rulemaking process.

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the ACS publication. However, it appears that the percentages of cancers associated with these causes is from Doll and Peto (1981). If so, it is important to note that Doll and Peto's analysis has a number of weaknesses which are well characterized in the 2008-2009 report on the President's Panel on Cancer, "Reducing Environmental Cancer Risk, What We Can Do Now," http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf. Specifically, it is now recognized that the development of cancer depends on multiple factors and that the contribution of environmental factors is likely underestimated in Doll and Peto's work. Doll and Peto relied primarily on epidemiologic studies of workers in large industries and failed to include minorities, deaths among persons aged 65 and older, exposures in smaller workplaces, and the effects of indirect contact with carcinogens. Even if Doll and Peto's suggested percentages were deemed to be accurate, given the population of the United States, the general probability of getting cancer, and the costs of cancer treatment, occupational and environmental cancer exacts a staggering cost to the U.S., as well as costs in human suffering that are difficult to quantify.

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6. The Idaho paper discusses the origins of use of one in a million risk (pg. 3). However, the origin of the use of one in a million risk is really not relevant if an analysis of the factors involved in developing risk based standards lead to use of this risk level (e.g. What is the appropriate risk level associated with criteria regulating involuntary exposure of all U.S. citizens to chemicals in the Nation's waters?). The focus should be on evaluation and discussion of the issues covered in the Idaho paper as limited by the enabling statute, the Clean Water Act, not the historical origin of one in a million risk.

7. In considering risk levels used by other regulatory programs (pg. 4), DEQ should define how risk is considered as specified in the enabling statutes and associated implementation regulations. Further considerations include whether or not risk is involuntary (as is the case for exposure to contaminants in environmental media) or is voluntary (as is the case for some occupational exposures). Another consideration is the scope of the program of interest (e.g.

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the limited geographic scope of CERCLA/RCRA cleanups, the national scope of ambient water quality criteria, or regulation of the workplace). A useful addition to the discussion paper would have been a discussion of how other entities have considered risk in setting water quality criteria as opposed to comparing risk levels across programs with varied regulatory objectives and mandates.

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We look forward to continued work with DEQ on this effort and are available if you would like to discuss our comments further. Please contact Lon Kissinger (206-553-2115) or myself (206-553-1834) if you have any questions.

Sincerely,

Lisa Macchio
Water Quality Standards Coordinator

Printed on Recycled Paper

01092

Subject: FW: EPA Comments on Idaho's Discussion Paper #7 Risk Management REALLY THIS IS THE FINAL VERSION

Attachments: EPA Comments on Discussion Paper #7 Risk Management FINAL.pdf

From: "Macchio, Lisa" <Macchio.Lisa@epa.gov>
Date: Wednesday, January 21, 2015 3:06 PM
To: "Don.Essig@deq.idaho.gov" <Don.Essig@deq.idaho.gov>, "jeffrey.fromm@deq.idaho.gov" <jeffrey.fromm@deq.idaho.gov>
Cc: "Kissinger, Lon" <Kissinger.Lon@epa.gov>, "Soscia, Marylou" <Soscia.Marylou@epa.gov>, "Chung, Angela" <Chung.Angela@epa.gov>, "Fleisig, Erica" <Fleisig.Erica@epa.gov>
Subject: RE: EPA Comments on Idaho's Discussion Paper #7 Risk Management REALLY THIS IS THE FINAL VERSION

I have to apologize for sending the incorrect version to you. Here is the FINAL version of our comments.

Lisa Macchio
U.S. EPA, Region 10 (OWW-131)
1200 Sixth Avenue, Suite 900
Seattle, WA 98101
(206) 553-1834
macchio.lisa@epa.gov

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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Seattle, WA 98101-3140

OFFICE OF
WATER AND WATERSHEDS

January 20, 2015

Don Essig
Idaho Department of Environmental Quality
1410 N. Hilton
Boise, Idaho 83706

RE: EPA comments on Idaho's Discussion Paper #7 Risk Management and Protection of Human Health

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the limited geographic scope of CERCLA/RCRA cleanups, the national scope of ambient water quality criteria, or regulation of the workplace). A useful addition to the discussion paper would have been a discussion of how other entities have considered risk in setting water quality criteria as opposed to comparing risk levels across programs with varied regulatory objectives and mandates.

8. The discussion paper's section on flexibility in choice of risk level (pg. 7) does not fully describe the recommended risk range for setting AWQC. The language within the paper focuses on use of 10^{-6} to 10^{-5}. However, EPA's Human Health Methodology (EPA 2000) notes that States and Tribes can choose more stringent risk levels, such as 10^{-7}.

9. The discussion of voluntary vs. involuntary risk (pg. 7) touches on the responsibility of government to reduce risks. However, the discussion paper does not address the important issue of environmental justice and how DEQ should consider those issues, recognizing that tribes and other low-income, minority populations have generally been well-documented to have exposures to contaminants in fish and shellfish exceeding those experienced by the general population. These issues, along with tribal trust responsibilities, including treaty rights, are important considerations. The conclusions section (pg. 8) should address these types of issues.

We look forward to continued work with DEQ on this effort and are available if you would like to discuss our comments further. Please contact Lon Kissinger (206-553-2115) or myself (206-553-1834) if you have any questions.

Sincerely,

Lisa Macchio
Water Quality Standards Coordinator

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REVIEW ARTICLE

Origin of the linearity no threshold (LNT) dose–response concept

Edward J. Calabrese

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Abstract This paper identifies the origin of the linearity at low-dose concept [i.e., linear no threshold (LNT)] for ionizing radiation-induced mutation. After the discovery of X-ray-induced mutations, Olson and Lewis (Nature 121(3052):673–674, 1928) proposed that cosmic/terrestrial radiation-induced mutations provide the principal mechanism for the induction of heritable traits, providing the driving force for evolution. For this concept to be general, a LNT dose relationship was assumed, with genetic damage proportional to the energy absorbed. Subsequent studies suggested a linear dose response for ionizing radiation-induced mutations (Hanson and Heys in Am Nat 63(686):201–213, 1929; Oliver in Science 71:44–46, 1930), supporting the evolutionary hypothesis. Based on an evaluation of spontaneous and ionizing radiation-induced mutation with *Drosophila*, Muller argued that background radiation had a negligible impact on spontaneous mutation, discrediting the ionizing radiation-based evolutionary hypothesis. Nonetheless, an expanded set of mutation dose–response observations provided a basis for collaboration between theoretical physicists (Max Delbruck and Gunter Zimmer) and the radiation geneticist Nicolai Timoféeff-Ressovsky. They developed interrelated physical science-based genetics perspectives including a biophysical model of the gene, a radiation-induced gene mutation target theory and the single-hit hypothesis of radiation-induced mutation, which, when integrated, provided the theoretical mechanism and mathematical basis for the LNT model. The LNT concept became accepted by radiation geneticists and recommended by national/international advisory committees for risk assessment of ionizing radiation-induced mutational damage/cancer from the mid-1950s to the present. The LNT concept was later generalized to chemical carcinogen risk assessment and used by public health and regulatory agencies worldwide.

Keywords Ionizing radiation · Linearity · Dose response · Risk assessment · Threshold dose response · Target theory · Eugenics · LNT

Introduction

In 1956, the US National Academy of Sciences (NAS) Committee on Biological Effects of Atomic Radiation (BEAR I)/Genetics Panel issued the most far reaching recommendation in the history of risk assessment that genomic risks associated with exposure to ionizing radiation should be evaluated with a linear dose–response model, no longer via the threshold dose–response model that had long been the "gold" standard for medicine and physiology (Calabrese 2005, 2009a, 2011). The Genetics Panel members believed that there was no safe exposure to ionizing radiation for reproductive cells with the mutation risk being increased even with a single ionization (Hamblin 2007). The LNT concept was generalized in 1958 to somatic cells and cancer risk assessment by the National Committee for Radiation Protection and Measurement (NCRPM) (Whittemore 1986). Quickly thereafter, other national and international advisory committees and organizations adopted such judgments for ionizing radiation (Calabrese 2009b). In 1977, the Safe Drinking Water Committee (SDWC) of the US NAS extended the linear dose–response risk assessment model of the BEAR/

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Biological Effects of Ionizing Radiation (BEIR) committees to chemical carcinogens, a recommendation that was soon adopted and implemented by the Environmental Protection Agency (EPA). On a parallel track, similar LNT risk assessment procedures were adopted by the Food and Drug Administration (FDA) in 1977 concerning animal carcinogen drug residues.

Despite the fact that the LNT model has been of central importance in chemical and ionizing radiation regulatory risk assessment, its origin is not within the environmental/occupational risk assessment domain. The current paper provides a novel historical assessment of the scientific origin of the LNT. It will show that the LNT was first applied to the field of biology in 1928 to explain the occurrence of genetic variation that would serve as the "biological engine" for evolution. The paper will also demonstrate how the linear dose–response model as proposed by Olson and Lewis (1928), which soon afterward became transformed into a "Proportionality Rule" by Muller (1930), became mechanistically framed within the context of a single-"hit" hypothesis based on the target theory by Timoféeff-Ressovsky et al. (1935) in a unique collaborative effort between leading theoretical physicists and radiation genetics. This paper extends two earlier publications within Archives of Toxicology concerning historical foundations of the LNT concept (Calabrese, 2009b) and threshold/hormetic (Calabrese 2009a) models.

Evolution and LNT

Since the publication of the Origin of Species in 1859 by Darwin and the rediscovery of the works of Mendel on gene inheritance, there was intense interest in the biological community to determine the cause of genetic change or novelty that would be subject to natural selection, thereby providing an important mechanism of evolution. As noted by Patterson (1933), a well-known colleague of Hermann J. Muller at the University of Texas/Austin, "the important question in biology is the problem of evolution" referring to the need to understand the mechanism of evolution at the gene level. Despite the fact that the gene was more of a concept than a physical entity during the early decades of the twentieth century, it was widely believed that the gene was the basic unit of heredity and that the driving force for evolutionary change must be via the induction of heritable genetic changes or mutations at the gene level (Muller 1922). This perspective provided the basis for intense interest by numerous genetics researchers in the second and third decades of the twentieth century to induce alterations in heritable traits by environmental (e.g., temperature) alterations, physiological stressors (e.g., starvation), as well as toxic chemicals and ionizing and non-ionizing radiation.

Given the central importance of evolution in biology and underscoring the intensity of the competition to be the first to demonstrate inducible heritable changes, Muller (1927) provided only an initial "discussion" of his mutagenicity findings with no data in his now famous *Science* paper that led to his Nobel Prize in 1946. This was done in order to secure recognition of being the first to report induction of heritable mutations by an environmental agent (i.e., X-rays). The supporting data were published the next year in a conference proceeding of very limited distribution based on the World Cat database (Muller 1928a) and also within the *Proceedings of the National Academy of Sciences* (PNAS) (Muller 1928b). Not only were the findings of mutation significant so too was the fact that the mutation rate was increased by about 150-fold at the highest dose tested.

Muller speculated that naturally occurring ionizing radiation might be a significant explanatory factor for genetic variation and may drive the evolution process. However, Muller was cautious in making the mutation–evolution link as the doses he had used to induce mutation were extremely high, exceeding background by about 200,000-fold, causing sterility or mortality in a substantial proportion of the fruit flies tested. In addition, the dose response was not linear but closer to a square root function due to a modest decline from linearity at the highest dose (Muller 1927, 1928a). If the true dose response for ionizing radiation-induced gene mutation was linear at low dose, as a general condition, then it may have explanatory implications for an evolution mechanism. Consequently, he soon directed several members in his laboratory to assess the topic of dose response more fully than he did in his groundbreaking mutation discovery. While the follow-up research by Muller's group was being undertaken, Axel R. Olson and the prestigious physical chemist Gilbert N. Lewis (1928) of the University of California/Berkeley published a proposal on April 28, 1928, in *Nature* that natural radioactivity was likely a significant cause of mutation that could generate variability from the parent generation and affect the process of evolution. These authors based this supposition on a report of January 1, 1928, in *PNAS* by Goodspeed and Olson on X-ray-induced heritable changes in tobacco. These authors claimed that the tobacco plant studies were specially planned to facilitate a direct comparison of mutation rates between the artificial X-rays and "naturally occurring radiations." Olson and Lewis (1928) also stated that "since the rays can only be effective when they are absorbed, and this produces ionizations, it seems safe to assume that the various rays will produce biological effects *in proportion to the ionization which they cause*" (emphasis added), a perspective based on the emerging target theory for radiation-induced biological effects proposed by leaders in the physics community (Glocker 1927; Crowther 1924).

Olson and Lewis (1928) then utilized a simple linear mathematical model to derive a mutation estimate at a selected natural background radiation dose. With this method, they estimated the number of variants (mutants) induced per year by natural radiation. These authors concluded that "it seems, therefore not altogether extravagant to assume that such variations as actually occur in nature are due largely to the radioactivity of the environment." The involvement of Gilbert Lewis in this activity, while unexpected, was derived from his research in the 1920s in the area of radiation physics (Coffey 2008). Furthermore, his eclectic research activities had also drawn him toward evolutionary theory, the subject of his major presentation (i.e., Silliman Lecture) at Yale, just preceding the development of the LNT paper in *Nature* (Lewis 1926). This lecture followed that of Thomas Hunt Morgan of Columbia University in 1925, Muller's Ph. D. advisor and 1936 Nobel Prize recipient. The perspective of Olson and Lewis (1928) was also independently advanced by Muller in a paper read before the National Academy of Sciences on April 24, 1928, and published on September 14, 1928. The statement of Muller (1928b) was principally conceptual, lacking the detailed formulation of Olson and Lewis (1928).

The following year, Babcock and Collins (1929a, b) tested the hypothesis of Olson and Lewis (1928). They found a location in which the natural radiation was twice that found in their University of California/Berkeley laboratory. Using the ClB strain sex-linked recessive *Drosophila* assay, they reported an increase in mutation that corresponded in the same proportion as the difference in background radiation, supporting the proportionality hypothesis. Detailed experimental methods including the actual radioactivity levels were never published, although such data were promised to be provided in a subsequent paper. In 1930, Hanson and Heys provided further support for the hypothesis that "natural radiation may be responsible for the mutations that are the grist of the natural selection mill with the resulting evolution of new forms." Their findings were based on a study of fruit fly mutations in an abandoned carnotite (i.e., uranium) mine. Such interpretations were initially supported by commentaries by various authors (Lind 1929; Dixon 1929, 1930).

In 1930 Muller and Rice University physicist, Mott-Smith, challenged this LNT evolution perspective by reporting that natural radiation, which was of such a low-dose rate, could only account for about 1/1,300 of the gene mutations that occurred spontaneously in *Drosophila melanogaster*, assuming a linear dose response. The authors concluded that other causes must explain the origin of most mutations that spontaneously occur. Nonetheless, in his dissertation, under the direction of Muller, Oliver (1931) stated that cosmic and terrestrial radiations must account for some proportion of the spontaneous mutations (see Muller 1930). This conclusion was justified on the belief that the response is linear at low dose, with there being no threshold for a mutation response. This relationship was stated as holding true for all types of high-energy radiation (e.g., gamma, beta, X-rays and probably ultra-violet rays). Thus, Oliver (1931) concluded that "by inference it can be added that the cosmic and the terrestrial radiations also are capable of producing mutations in proportion to their power of ionization." Oliver (1931) also extended the concept of proportionality to chromosomal inversions and translocations further arguing for the support of a background radiation influence. For example, Muller and Altenburg (1930) noted that translocations are induced at a similar frequency as gene mutations. Given these circumstances, Oliver (1931) noted that "one would expect each of the classes of changes considered to occur with the same frequency when the individuals are subjected only to the natural conditions, if natural radiation can account for all mutations…" Despite this interpretation of environmental radiation-induced genetic changes, Oliver (1931) concluded that "some other condition must, therefore, enter in order to explain the difference in non-radiated material, between the frequency of gene mutation and that of the other type of genetic changes." (p. 34)

Even though Muller dismissed natural radiation as providing a quantifiably significant mutational influence to derive genetic novelty for evolutionary change, he still retained his belief in the linear dose–response relationship (p. 238) (Muller 1930) based on the findings of Hanson and Heys (1929, 1930) and Oliver (1930). Even though the hypothesis of Olson and Lewis (1928) did not maintain significant support for long within the scientific community, Muller and other leaders of the radiation genetics community became strong advocates of the LNT model to account for genomic mutations and the occurrence of cancer.

It may seem difficult to understand in retrospect why prominent scientific leaders such as Gilbert N. Lewis, Hermann J. Muller and others so quickly adopted a belief in linearity at low dose. In the case of Muller, he was fully committed to this view after the publication of only three studies (Hanson and Heys 1929, 1930; Oliver 1930) in which the lowest cumulative dose was roughly 285 r, administered in an acute manner, the rough approximation of 1,000 modern chest X-rays in 3.5 min or 5 chest X-rays/s.

In his rather copious publications during this period of "belief"/concept formulation, Muller never addressed contemporary publications that did not support a linear interpretation (Patterson 1928; Weinstein 1928; Stadler 1930, 1931). Yet, he was well aware that the lowest doses in the Hanson and Heys (1929, 1930) and Oliver (1930) papers were acute studies that grossly exceeded background radiation exposure. To think within a linear dose–response term

framework ran counter to pharmacological and chemical toxicological experience at that time. As Zimmer (1966) reflectively wrote, toxic chemicals in the early decades of the twentieth century demonstrated "no effect up to a threshold dose and then climbed steeply up to 100 %." Muller and others argued that the genetic response to ionizing radiation demanded a different evaluative framework.

Target theory and LNT

A likely explanation for Muller's (and possibly Gilbert N. Lewis's) acceptance of the LNT in the absence of convincing dose–response data may be found within the scientific culture at the time. X-ray-induced mutational effects were placed within the context of what was called the radiation target theory. This theory was quantitative and dosimetric, with mathematical calculations related to quantum mechanics, reflecting the leadership of prestigious theoretical physicists (von Schwerin 2010). The formation of a physics-based target theory was established prior to the discovery of inducible mutations by Muller (1927) by medical physicists such as Dessauer (1922), Glocker (1927) and Crowther (1924, 1926, 1927), setting the stage for a novel scientific framing of the mutational data in the 1930s. The mutation findings of Muller (1927) were a major scientific advance that easily fit into the target theory concept while also markedly advancing the scientific standing of target theory itself.

The radiation target theory as applied to mutations was formulated by the detailed interactions and collaborations of leading radiation geneticists and theoretical physicists during the mid-1930s. During this time, radiation geneticists, lead by Nicolai Timoféeff-Ressovsky, and physicists, including Niels Bohr, with a profound interest in the interface of physics and biology, would meet each year, typically in Copenhagen and Belgium for extensive discussions. From these exchanges developed the seminal conceptual paper by Timoféeff-Ressovsky and the physicists Max Delbruck and Kevin Gunter Zimmer (Timoféeff-Ressovsky et al. 1935) that would establish a conceptual framework for gene structure, target theory for the induction of mutations via ionizing radiation, the single-hit mechanism hypothesis to account for the shape of the LNT dose response and the application of this dose–response model for what was to become modern cancer risk assessment. The genetic target theory saw mutation as a purely physical action following an all or none law in which a single ionization or energy absorption produces the mutational effect independent of all other ionizations and energy absorptions.

This linearity feature stands in contrast to normal physiology that invariably deals with large numbers of molecules of each kind, and where the elimination of a single molecule would not result in observable effects (Delbruck 1940). The energy of ionizing radiation was assumed to be essentially transformed into a genetic effect. According to the physicist turned biologist Max Delbruck (1969 Nobel Prize recipient in Biology and Medicine), the proportionality rule that was proposed earlier by Muller, based on the research of Hansen and Heys (1929) and Oliver (1930, 1931) and supported in experimental research by Timoféeff-Ressovsky et al. (1935), provided the basis of the single-hit mechanism interpretation and the calculation of the size of the gene (Delbruck 1940). Table 1 provides a listing of quotes in which the early conceptual framing of the dose–response proportionality concept occurred. The transforming of a dose–response hypothesis based on a very limited amount of data into a biological "Rule" by Muller was done without significant discussion of the concept, its possible mechanisms as well as the recognition of data that may contradict this "Rule."

Although Muller was a geneticist, he was drawn quickly toward the physics-mutation interface, accepting significant elements of target theory for radiation-induced mutational effects, including the important assumptions that damage was proportional to the energy absorbed, linear dose–response modeling and that effects were cumulative and deleterious (Muller et al. 1936). Muller knew Timoféeff-Ressovsky, having met him in the Soviet Union in 1922, encouraging him and his colleagues to transform his laboratory to one of the *Drosophila* genetics. Muller renewed contact with Timoféeff-Ressovsky during the 5th International Congress on Genetics in 1927. From November 1932 to September 1933, Muller researched in Berlin with Timoféeff-Ressovsky. He also participated in the physics-biology/mutation discussions in Copenhagen in 1936, engaging Niels Bohr and other leading physicists. Experiments of radiation geneticists during this period were often designed within the context of this target theory framework. This was also the case for critical studies performed a decade later under the aegis of the Manhattan Project at the University of Rochester under the direction of Curt Stern (with Muller serving as a consultant) (Spencer and Stern 1948; Caspari and Stern 1948).

The hit hypothesis

As noted above, in his Nobel Prize research, Muller reported that the induction of mutations was not directly proportional to the X-ray dose, but rather to the square root of the dose (Muller 1927). Based on discussion with the physicist and future Nobel Prize winner Irving Langmuir (1932 Nobel Prize in Chemistry), Muller (1927) stated that this observation suggested that the induction of mutation was not caused directly by a single quantum of energy.

Table 1 Documentation of the introduction of the proportionality rule concept into the mutation literature, 1929–1960

References	Quote
Hanson and Heys (1929)	"It is only to be expected that the number of mutations be directly *proportional* to the number of rays to which the organisms are exposed." Page 207
Muller (1930)	"Since then Hanson, using radium, and Oliver in our laboratories using X-rays, have both found that the frequency of mutations produced is exactly *proportional* to the energy of the dosage absorbed… There is, then, no trace of a critical or threshold dosage beneath which the treatment is too dilute to work." Page 236
Oliver (1930)	"That is there is a direct *proportionality* between the percent of lethals and the length of time of treatment may be seen more readily by a comparison of the t_1 values calculated from the results for each of the given doses." Page 45
Stadler (1930)	"Mutation frequency increased approximately in direct *proportion* to dosage." Page 13
Hanson et al. (1931)	"Taking the amount of ionization in air as a measure, the mutation rate seems to vary approximately in direct *proportion* to the intensity." Page 142
Oliver (1931)	"By inference it can be added that the cosmic and the terrestrial radiations of higher energy content also are capable of producing mutations in *proportion* to their power of ionization." Page 480
Oliver (1931)	"The relation of *proportionality* to the dosage applies not merely to the lethals in general, but, more specifically, to the lethal gene mutations." Page 485
Oliver (1931)	"…[gene mutations and gene rearrangements] all probably occur in direct *proportion* to the dosage, no matter how small a dose is used." Page 486
Patterson (1931)	"In general their results [i.e., Hanson and Heys 1928 and Oliver 1930] justify the conclusion that the rate is directly *proportional* to the dosage employed." Page 133
Hanson and Heys (1932)	"Further evidence of the *proportionality rule* from a study of the effects of equivalent doses differently applied." Page 335
Hanson and Heys (1932)	"Experiments planned with a view to determining within what limits the *proportionality rule* holds show again a strict correspondence existing between the amount of radium administered and the consequent biological effect, the induced mutation frequency obtained varying directly with the dosage." Page 343
Hanson (1933)	"The rate seems to be directly *proportional* to the dosage. Muller has named this the '*proportionality rule.*' For example, when all other factors are kept constant, doubling the time of exposure also doubles the number of lethal mutations." Page 486
Oliver (1934)	"The frequency of induced mutations is directly *proportional* to the intensity of the treatment." Page 391
Delbruck (1940)	"The *proportionality rule* gave the basis for the single-hit interpretation…" Page 359
Stern (1950)	"The *proportionality rule* has been proven to hold over a wide range. Figure 155 shows that, for Drosophila, the relation is essentially linear over the range from 25 r to several thousand r. It has further been shown that the frequency of induced mutations is independent of the time over which the radiation is applied." Page 433
Stern (1960)	"It has been established for a variety of experimental organisms that the number of mutations induced by radiation is proportional to the dose. This *proportionality* has been proven to hold over a wide range of dosages." Page 491

However, subsequent exposure experiments by Hanson and Heys (1929), Oliver (1930, 1931) and later by Timoféeff-Ressovsky et al. (1935), even though all experiments were at very high dose, supported a proportionality relationship, which was consistent with the "hit" theory of mutation in which the X-ray treatment excites an electron in the target gene. This excitation was proposed to affect a permanent change or mutation to a different molecular structure. Ionizing irradiation was the only effective way to induce mutations; it showed no threshold, suggesting that the absorption of radiation is a quantized and additive process (von Schwerin 2010). A "quantum-jump" was considered to be the physical process caused by a hit on a target, resulting in mutation. Treatment effects induced by a physical agent like ionizing radiation were believed to be caused by one or several discrete biophysical events, that is, hits on a target. Based on hypotheses about what constituted a hit, statistical models were used to construct dose–response relationships. If there was only a single hit on a single target, the dose response was linear. As the number of assumed hits increased, a more threshold like the dose response would appear. In a practical sense, the mathematical model-derived dose response based on an assumed number of hits could be visually matched against the laboratory-obtained dose–response curve. Using this direct and simplified approach, researchers like Muller, Timoféeff-Ressovsky and participating physicists decided the theoretical number of hits. This type of target theory was especially strong in Germany, with support from leaders such as Boris Rajewsky (Director of the KWI for biophysics, 1936), Timoféeff-Ressovsky and others (von Schwerin 2010). This conceptual framework led to the conclusion that mutation was a

single-hit process, proceeding from a single ionization, from a quantum of ionizing radiation in a specific sensitive zone of the gene.

This theoretically based perspective became not only a workable model but a firm belief within the radiation genetics community even though there was no knowledge of the physical nature of the gene. As coauthor of the Timoféeff-Ressovsky et al. (1935) paper, Delbruck subsequently noted in his Nobel Prize lecture that it was thought that genes were very stable and, therefore, showed characteristics of molecules. However, the gene concept at that time was simply that of Mendelian algebraic rates, lacking structural chemistry insight. There was much speculation of gene structure including that of submicroscopic steady-state systems or even an entity not readily analyzable in chemistry as proposed by Bohr (1933).

The paper of Timoféeff-Ressovsky et al. (1935), as noted above, was striking in its collaboration between physics and genetics, its proposed chemical nature of the gene, size of the gene and in the proposal of a "hit" hypothesis as the foundation of the linear dose response for ionizing radiation-induced mutation. While the gene structure and size framework would be bypassed and replaced by the DNA structure of Watson and Crick (1953), the hit theory component of Timoféeff-Ressovsky et al. (1935) was accepted and implemented by the radiation genetics community. The term "hit hypothesis" became commonly used in the lexicon of radiation genetics, including those comprising the BEAR I Committee/Genetics Panel that recommended changing to a linear model from a threshold model for assessing mutation risks from ionizing radiation (Calabrese 2013).

The impact of this 1935 article was facilitated by the actions of Timoféeff-Ressovsky who sent reprints to key researchers. However, the overall immediate impact of the paper was very limited as it was published in an obscure Gottingen journal that was not cited in any leading index with only four issues being printed before ceasing publication. This paper, which provides the origin of the single-hit hypothesis to support a linear dose–response model, was not even cited in the BEAR I report that implemented the concept. Yet, the term "hit" hypothesis and target theory became commonly used, even if credit was not often given to the original paper (Timoféeff-Ressovsky et al. 1935). Nonetheless, this paper did receive a major endorsement in the 1944 book *"What is Life"* by Erwin Schrodinger, a Nobel Prize physicist (1933), raising its visibility in the physics community.

The concept of the gene and its striking stability suggested it must have a unique atomic composition. Delbruck (1970) believed that such stability might be due to each atom of a gene being fixed in its mean position and electron-stable, sunk in an energy well, now seen having stability due to the function of the hydrogen bond. Mutations of such genes could only occur following the absorption of high energies as from ionizing radiation, not from heat under physiological conditions. In fact, a modest increase in vibrational energy was estimated to increase the atomic stability, decreasing mutational risk. Since a transaction in an atom can be affected by a single digit eV and that the initial impact of an X-ray can be several fold greater, it was believed that any gene would be at risk for mutation from radiation. Since the initial energy of impact exceeds a threshold energy of activation, ionizing-radiation should affect not only the induction of a localized mutation but also that of a broad range of gene targets.

The mutation hit theory was challenged by Caspari and Stern (1948) in a chronic, very low-dose rate study, leading to the hypothesis that either a threshold exists or multiple independent primary actions are required for a mutation to occur, or that a recovery or repair effect/process occurred at a very low-dose rate (Howarth et al. 1950; Key 1951). Over the next several decades, the dominance of the physics-based target theory would yield to improved chemical/biological/physiological understandings of the mutation process, including such modified target theory effects of ionizing radiation as DNA repair (in reproductive and somatic cells), adaptive response, the bystander effect as well as the recognition that the biological effects of ionizing radiation are principally due to the generation of hydroxyl radicals/hydrated electrons from cellular water and their migration to cellular targets (Collinson et al. 1962; Czapski and Schwartz 1962; Weiss 1944). In fact, even as the target theory was being applied to mutation by Timoféeff-Ressovsky et al. (1935), the recognition of repair processes, including DNA repair, were emerging (Hanawalt 1994). Such challenges to the hit theory would eventually be brought to the BEAR Committee by Russell (1956, 1963) from Oak Ridge, but only after the BEAR 1 Committee made its linearity recommendation.

Edward Lewis (1957a), another radiation geneticist Nobel Prize (1995) recipient, published a very influential *Science* article in 1957, strongly supporting a linear relationship for cancer, relying on linearity data in the Uphoff and Stern (1949) paper. In subsequent Congressional Testimony, Lewis (1957b) would argue that the dose response was linear, regardless of the mechanism, and should be accepted as such whether or not a mechanism could even be discerned. These comments of Lewis suggested that he recognized the growing mechanistic challenge to the single-hit theory as well as new conceptual problems (e.g., multiple biological processes could yield a linear relationship that did not require a single-hit process) emerging from the physics and genetics communities, including Zimmer (1941), a coauthor of the Timoféeff-Ressovsky et al. (1935) paper and radiation biologists/geneticists (Haas et al. 1950;

Kimball 1952). However, the time period within which Muller's mutation findings were produced was one of the cultural scientific dominance of physics. Association with the leadership of the physics community served to enhance the significance of the mutational findings and its assumed linearity at low dose, as well as providing Muller with an expanded scientific and cultural context that recognized his achievements and enhanced his scientific reputation.

The influence of the hit concept of Timoféeff-Ressovsky et al. (1935) was facilitated via subsequent publications of Lea (1940, 1946), which offered further justification for the target theory-based LNT-single-hit hypothesis for mutation. The publications of Lea were not only authoritative extensions of Timoféeff-Ressovsky et al. (1935) but more readily available than the Timoféef-Ressovsky et al. (1935) paper with its publication in a defunct journal.

Regulatory agency actions

Ionizing radiation

In the radiation risk assessment area, two endpoints were adopted to which linearity was applied: germ cell mutations and cancer. In the case of germ cell mutations, based on several publications in the early 1950s by Muller (1951, 1954), the BEAR I Genetics Panel (1956) proposed to limit exposure to ionizing radiation such that exposure would not exceed doubling of background mutations from conception through the first 30 years of life. The panel assumed that exposure to ionizing radiation could cause mutations to germ cells in a linear manner and had the potential to cause adverse genetic effects in individuals and future generations. The panel derived a risk assessment methodology for application to both first-generation offspring and total genetic risk, including future generations. The panel derived a doubling dose method (i.e., the dose of ionizing radiation, assuming linearity at low dose, that would equal the number of mutations resulting from background exposure), to estimate population-based risks. This doubling dose methodology would predict the number of genetic diseases based on three parameters: the assumed doubling dose, the proposed exposure limit and the background incidence of genetic disease. Based on this risk assessment framework, the panel recommended a "uniform national standard" such that the members of the general population would not receive more than a cumulative dose of 10R from conception through 30 years. This basic method of the BEAR I Committee, using the doubling dose/linear framework, has been refined with recent advances allowing one to integrate between rates of radiation-induced mutation based on mouse studies and the risk of inducible genetic disease in people [Sankaranarayanan and Chakraborty 2000a, b; Sankaranarayanan and Wassom 2008 (see Lyon 2003 for an alternative view)].

In the case of somatic effects, cancer risks were estimated via the use of a linear dose–response model. Assuming linearity to zero, it was estimated that exposure of one rem to one million people each year would cause one to two new cases of leukemia on an annual basis for first decade of life (ICRP 1962; Sowby 1965; UNSCEAR 1962, 1964). As with chemical carcinogenesis risk assessment, therefore, the foundations of the LNT modeling for ionizing radiation-increased cancer risks are directly traced back to Lea, Timoféeff-Ressovsky et al. and ultimately to Muller's proportionality rule.

Chemical carcinogens

Five years after the publication of the BEAR 1 report, Mantel and Bryan (1961) published their influential paper entitled "Safety' Testing of Carcinogenic Agents" based on the probit dose–response model in order to estimate tumor incidence for carcinogens. Biostatistical estimates of cancer risks were first provided by Bryan and Shimkin (1943) when they applied the probit model to estimate the cancer risk of three carcinogenic hydrocarbons (i.e., 20-methylcholanthrene; 1,2,5,6-dibenzanthracene; 3,4-benzpyrene) in strain C_3H male mice.

The motivation for Mantel and Bryan to develop the biostatistical model for predicting carcinogen risk was due to the fact that Mantel, a biostatistician at the US National Cancer Institute (NCI), was asked by the Director of the NCI to develop guidelines for the number of laboratory animals that would be needed to establish the safety of a test agent within the context of a hazard assessment. This response followed a request, after the Thanksgiving cranberry scare of 1959, by the Secretary of the Department of Health, Education and Welfare (HEW) to the NCI. The cranberry scare was a public relations nightmare in which trace residues of a cancer-causing herbicide [i.e., amitrole (3-amino-1,2,4-triazole)] were detected in some sources of cranberries just before the holiday. The secretary of HEW recommended against buying cranberries that year, leading to a consumer panic that threatened the industry. In order to avoid such situations in the future, the secretary of HEW requested the NCI to provide guidance on which cancer-causing substances were "safe" and at what dosage levels.

Mantel and Bryan (1961) noted the generality of their modeling approach and proposed the concept of a virtually safe dose with an estimated risk of 1/100 million. Some 12 years later, the FDA would propose the use of the Mantel-Bryan (1961) model and recommend the 1/100 million safety guide in their July 19, 1973 risk assessment proposal in the Federal Register. When the rule was finalized in

1977, the Mantel-Bryan probit model was retained but with several modifications and with the acceptable (de minimus) risk being reduced to 1/million. This value was considered as the level below which no additional regulatory action would be taken within the context of the safety of animal carcinogen residues. The finalized Mantel-Bryan model of the FDA was the first quantitative risk assessment model approved by a regulatory agency. Two years later, the FDA (1979) significantly revised the cancer risk assessment policy, replacing the modified Mantel-Bryan model with a linear dose–response model based on multiple factors, including its more conservative risk estimation and ease of calculations (Anonymous, 1979). In the low-dose zone, the one-hit model discussed above is closely approximated by a simple linear model.

The US EPA strategy for assessment and regulation of carcinogens displayed a profound evolution during the 1970s. Based on expert testimony during pesticide hearings, EPA attorneys developed a legal brief that embodied "cancer principles" (NAS 1983). These "principles" suggested that carcinogen exposures should be prevented. As the concept of "banning" carcinogenic agents was soon seen as unrealistic, EPA quickly adopted non-regulatory guidelines for a general risk assessment process (EPA 1976). This process advocated the use of quantitative risk assessment as a means to differentiate risks among chemicals and engineering processes. The guidance was very general, being limited to less than a page within the Federal Register. These guidelines were followed by a paper from the EPA Carcinogen Assessment Group (CAG) (Albert et al. 1977), which provided a strong endorsement of the LNT concept, arguing that linearity was supported by human epidemiological studies (e.g., ionizing radiation and cigarette smoking related lung cancer) and mutagenicity studies that were also claimed to follow a linear dose response and believed to be the underlying mechanisms of carcinogenesis. In a March 15, 1979, Federal Register, the EPA Administrator Douglas Castle stated that "Risk assessment from animal data is performed using the 'one-hit' model" based on the 1976 Interim Guidelines (EPA 1976). He went on to state that "the one-hit model was endorsed by the four agencies in the Interagency Regulatory Liaison Group" based on its highly conservative nature and the uncertainties in extrapolating from animal data to human responses and the possibility that humans may be more susceptible than the animal model, because of broad human interindividual variability in exposures and "other unknown factors". The strongly clarifying and underlying statement of the administrator was due in part to the fact that EPA had used other cancer risk assessment models under other regulatory acts and by other US federal agencies.

According to Albert (1994), Chair of the EPA Cancer Assessment Group (CAG) during the 1970s, the EPA adopted the linear no threshold model (LNT) of the Atomic Energy Commission (AEC) that had been applied to estimating risks from fallout from atomic weapon tests. The LNT model was attractive to EPA since it was very simple to apply; all that was needed in a toxicological sense was to identify the lowest dose of agent that induced a statistically significant response and draw a straight line to the origin of the graph for the dose versus cancer incidence. Its biological plausibility was based on the linearity of mutation dose response within the framework of target theory. He noted that "any difference between chemical carcinogens and ionizing radiation could be waived aside as they both cause genetic damage…"

Statisticians would argue that the straight line extrapolation to zero from the lowest statistically significant response ignored data at the high doses. Thus, during a meeting of leading statisticians called by the CAG, a decision was made to change from the single-hit model to the multi-stage model since it used all the data, while retaining linearity at low dose and being compatible with the concept of cancer being a multi-stage process. Consistent with this assessment, the NAS Safe Drinking Water Committee (1977) recommended the adoption of LNT modeling for risk assessment using a multi-stage model. However, in 1982, the Safe Drinking Water Committee (SDWC) was skeptical about LNT modeling for chemicals and rescinded its endorsement of the LNT model noting "…more confidence could be placed in mathematical models for extrapolation if they incorporated biological characteristics of the animal studies… since the users of this volume will be likely to favor different varieties of the conventional extrapolation models or will have access to some of the newer developmental methodologies, it is premature at this stage to recommend any single approach by selecting it for calculations…" (p 8). However, since LNT modeling was already in use by EPA, in 1983, the SDWC again endorsed the LNT model and its subsequent use became the default methodology for chemical cancer risk assessment. According to Albert (1994), none of the possible models (single hit, multi-hit, logit, probit, multi-stage, others) were biologically credible. The agency simply needed one that would be acceptable. The agency applied LNT risk assessment methods using the multi-stage model for the regulation of trihalomethanes in drinking water in a November 29, 1979, notice in the Federal Register (EPA Environmental Protection Agency (US EPA) 1979a, b), a process that would be followed in subsequent EPA cancer risk assessments.

The parallel, yet converging linear dose–response strategies of the EPA and FDA represent the regulatory origin of current cancer risk assessment practices throughout the world. They are directly traced back to the efforts of Lea (1946) and Timoféeff-Ressovsky et al. (1935), all of which stemmed from the "Proportionality Rule" of Muller (1930).

Eugenics

While the LNT concept for mutation was born within the intellectual and scientific framework of the physics-based radiation target theory, its applications also found supportive resonance within the philosophical, ideological and political frameworks of eugenics. German eugenicists expressed considerable concern that ionizing radiation may hurt the German germ plasm (Proctor 1999; Martius 1931). Educational programs based on these concerns cautioned against exposures to ionizing radiation that might adversely affect future generations of Germans. Recommendations as early as 1927 by the Bavarian Society for Pediatrics and Gynecology stated that women receiving excess X-rays during pregnancy should abort their fetuses. Pushing this concept even further, in 1930, Eugene Fisher, director of the Kaiser Wilhelm Institute for Anthropology, argued that women exposed to X-rays should be permanently prevented from having children (Proctor 1999). Muller's own history is replete with his highly visible association with national and international activities advancing eugenics philosophy and agenda. Even as late as 1955, Muller gave a strong eugenics advocacy presentation in Germany, testing such ideas with a large audience of Nobel Prize winners (The Lindau Mediatheque 1955).

The biophysical concept of the gene had important eugenics implications. Since mutations could be induced by ionizing radiation in a linear at low-dose manner, this concept provided the principal foundation that all ionizing radiation—whether via medical diagnosis/treatment or industrially—was a concern for "genetic health". The genetic toxicology studies of Timoféeff-Ressovsky et al. (1935) transformed these above-cited radiation health concerns, providing biophysical models and the LNT-single-hit model risk assessment paradigm. Such actions provided a key vehicle by which eugenics would focus on radiation protection for preventing the occurrence of genetic defects. In fact, the development and activities of the genetics department of the Kaiser Willheim Institute under the direction of Timoféeff-Ressovsky was affected by such perspectives (Gausemeier 2010).

The concept of LNT for ionizing radiation-induced mutation was, therefore, built upon a scientific/cultural framework and applied to a range of health-related policies, especially those of eugenics during the early decades after the discovery of X-ray-induced mutations. In fact, the eugenics area would serve as an intellectual training ground for how ideas such as LNT could be "softened", humanized and successfully integrated within a post-World War II society. Some aspects of eugenics advocacy and the LNT concept would morph into modern regulatory policy for carcinogen regulation, evolving from that of preserving the gene pool of certain racial subgroups or other targeted populations to a humanistic framework that would reduce mutational risks to entire populations.

Evolution and endogenous mutations

The LNT had its start in an attempt to explain evolution, finding other outlets in the world of eugenics and later public health regulatory policies. While Muller was a leader in these activities, he did not abandon his quest to determine those underlying factors that served to provide the novel mutations for natural selection. In fact, prior to his discovery of X-ray-induced mutations in 1927, Muller reported that temperature increases enhanced the mutation rate by about two-fold (Muller 1928c). However, the temperature hypothesis was placed on the research back burner when high doses of X-rays were found to markedly enhance mutation frequency. Muller would return to the temperature–evolution hypothesis some three decades later, completing an intellectual and professional circle, reflected in the comments of Plough and Ives (1934), his former colleagues at Amherst College (1940–1945) who noted that "since Muller and Mott-Smith conclude that natural radiation is inadequate to account for mutations in nature, it seems possible to suggest that ubiquitous temperature variations may play that role". If Muller had lived into the decades of the 1980s (he died in the 1967), he would have begun to appreciate the so-called other conditions suggested by Oliver (1931) as the cause of the overwhelming proportion of spontaneously occurring mutations is now believed to be derived from endogenous metabolism, for which complex and integrative DNA repair processes have been selected for via natural selection (De Bont and van Larebeke 2004; Lindahl 1996).

Summary

The LNT concept was initially proposed to account for evolutionary change and then later applied for the assessment of risks for some genetic diseases and cancer incidence (Table 2). The initial data upon which the LNT concept was based were limited to a few studies of an acute nature and at very high doses. Within a decade, the LNT dose–response model was provided with a mechanistic foundation via the integration of the single-hit concept within target theory. The LNT-single-hit model was then used by radiation geneticists to frame the intellectual debate on low-dose ionizing radiation risk to the human genome. It provided the basis for the recommendations of the US NAS BEAR I Committee in 1956 for

Table 2 LNT history: the temporal sequence leading to the LNT dose–response model for cancer risk assessment

References	Specific temporal events
Muller (1927)	Mutation findings—X-rays induce mutations in fruit flies ⇓
Olson and Lewis (1928)	LNT model proposed to account for evolutionary changes following Muller's discovery that X-rays can induce mutations in fruit fly germ cells ⇓
Muller (1930)	Develops proportionality rule (i.e., linear dose response) for ionizing radiation-induced mutagenicity ⇓
Timoféeff-Ressovsky et al. (1935)	Application of radiation target theory for mutagens. Used target theory to propose a hit theory for ionizing radiation-induced mutation. The hit mechanism was used to explain the LNT dose response ⇓
BEAR I 1956 (Biological Effects of Atomic Radiation Committee, Genetics Panel)	Proposes the use of the linear dose–response model for germ cell mutation, using the "doubling rule" ⇓
Mantel and Bryan (1961)	Develops carcinogen risk assessment model based on the probit model. This activity was undertaken to advise US governmental agencies on chemical risk assessment ⇓
FDA (1973)	Proposes a probit-based quantitative risk assessment method for cancer risk based on the Mantel and Bryan 1961 paper. The proposal stated that an acceptable risk was 1/100 million ⇓
EPA (1976) (see Albert et al. (1977), Anonymous (1979)	Proposed guidelines for carcinogen risk assessment based on quantitative risk assessment. Recommended a linear dose–response model ⇓
FDA (1977)	FDA rule finalized, retaining the Mantel-Bryan model with some modifications. The acceptable risk value was changed to 1/1 million (10^{-6}) ⇓
U.S. NAS Safe Drinking Water Committee (1977)	Recommended that EPA adopt LNT for carcinogen risk assessment. This recommendation was profoundly significant given the widespread multimedia regulatory functions of EPA. Within 2 years of the recommendation, EPA applied the LNT to the regulations of trihalomethanes (e.g., chloroform) in drinking water ⇓
FDA (1979)	Replaced the modified Mantel-Bryan model with the LNT model for carcinogen risk assessment, based on the following reasons: 1. Linear procedure is least likely to underestimate risk. 2. Linear extrapolation does not require complicated mathematical procedures. 3. No arbitrary slope is needed to carry out linear extrapolation. 4. Several significant limitations were found with the application of the Mantel-Bryan model (Anonymous 1979) ⇓
EPA (1979a, b)	EPA established a national drinking water standard for trihalomethanes (including chloroform) based on an LNT methodology as recommended by the US NAS Safe Drinking Water Committee (1977)

the switch from a threshold to a linear dose–response model for estimating ionizing radiation-induced germ cell mutation using the doubling dose concept. The LNT-single-hit model was soon generalized to the process of cancer risk assessment and adopted by national and international committees concerned with ionizing radiation by the late 1950s and early 1960s. Five years later, Mantel and Bryan (1961), researchers at the US National Cancer Institute, proposed a probit model-based cancer risk assessment method. It was the Mantel and Bryan (1961) model that was proposed by the FDA in 1973 for cancer risk assessment procedures, being replaced with a LNT model by the FDA in 1979, the same year that EPA applied the LNT for the regulation of carcinogens (i.e., trihalomethanes) in drinking water. The LNT model and its single-hit explanation/mechanism theory, therefore, can be traced back to the concept of radiation-induced mutation target theory as proposed by Timoféeff-Ressovsky et al. (1935), which was founded on the proportionality rule of Muller (1930) which itself had its origins in the 1928 paper of Olson and Gilbert that created the LNT concept following the seminal findings of Muller (1927) that ionizing radiation could induce mutation in the germ cells of fruit flies.

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Public officials shoulder the responsibility of determining which involuntary threats to human health are unacceptable and which are acceptable. For example, how much exposure to a cancer-causing chemical, if any, should be regarded as acceptable for regulatory purposes? In this issue of RISK IN PERSPECTIVE, we offer a historical perspective on this question as well as some principles that should govern future decisions.

The Demise of the "Safe" Dose

Early thinking about acceptable risk was contributed by regulatory toxicologists, who suggested that "safe" levels of human exposure to chemicals could be defined. While virtually all chemicals are toxic at sufficiently high doses, many toxicologists believe in the concept of a "threshold" dose below which no one will be harmed. Laboratory experiments are undertaken to determine the highest level of exposure to a chemical that does not have an adverse effect on test animals. This no-observed-adverse-effect-level (NOAEL) is then divided by a safety factor of 100 or 1,000 to determine the "safe" human dose.

While the concept of a "safe" dose continues to have substantial support today, many scientists believe the concept is not applicable to cancer-causing chemicals. On the basis of radiation biology and epidemiology, it has been hypothesized that any exposure to a cancer-causing chemical is associated with some increase in the probability of tumor formation. If chemicals cause tumors through direct interaction with DNA (so-called "genotoxic carcinogens"), the relationship between dose and response may have no threshold. Although cells can repair damage to DNA, these mechanisms may not always be 100 per cent effective.

Even if carcinogens exhibit threshold doses, the levels may be too small to be helpful to regulators. People are exposed to numerous chemicals from natural and man-made sources, and this background exposure may exceed whatever threshold exists for a particular cancer-causing mechanism. Moreover, some people may be more susceptible to cancer than others, which means that background levels of exposure may already exceed thresholds for those individuals in the population who are particularly susceptible to cancer. On the basis of these arguments, some scientists emphasize that background levels of exposure to cancer-causing agents are already initiating the carcinogenic process.

De minimis Risk at FDA

The emerging notion of "non-threshold" chemicals challenged regulators at the Food and Drug Administration, who are responsible for guaranteeing the safety of the nation's food supply. How much of a carcinogenic food additive, if any, should be permitted in meat?

During the 1970's, the FDA recognized that some procedure would be necessary to quantify low-dose cancer risks from meat additives and to determine a degree of risk that could be regarded as "essentially zero." FDA rejected detectability as a standard for safety because serious health risks might exist below chemical detection limits and detection technologies were improving rapidly.

FDA's earliest proposal was to use animal data and a probit model to define a "virtually safe dose" that was associated with an incremental lifetime cancer risk of 1 in 100,000,000. Later, FDA replaced the probit model with a linear dose-response model, which was considered more protective than the probit model. When switching to the more protective dose-response model, FDA determined that a risk level of 1 in 1,000,000 would be adequate to protect public health. FDA considered but rejected 1 in 10,000 as an "essentially zero" level of excess cancer risk. Note that if 200 million Americans were each exposed to a meat additive that posed an 1-in-10,000 lifetime risk, 20,000 excess cases of cancer would be predicted over a lifetime. This

01110

example illustrates that the size of the exposed population, as well as the level of individual risk, need to be considered by public officials.

The federal courts have upheld the authority of regulatory agencies to define *de minimis* levels of risk from exposure to toxic chemicals unless the statute in question compels zero risk. The Delaney Clause, for example, effectively compels the federal government to set zero tolerance levels for any cancer-causing additive that concentrates in food. Agency efforts to permit risks as large as 1-in-1,000,000 from color additives and selected food additives have been overturned by federal courts. Given the impracticality of the zero-risk standard, Congress is now considering legislation to modernize the Delaney Clause.

Significant Risk at OSHA

In the late 1970's the Occupational Safety and Health Administration proposed a generic standard for identifying and regulating chemical carcinogens in the workplace. The proposal called for reduction of all carcinogenic exposures to the lowest levels that are technologically and economically feasible, regardless of the number of workers exposed or the size of the risks to workers. A "carcinogen" was defined as any chemical that has been shown to cause cancer in one sound study of animals or people. Industry petitioners challenged OSHA's emerging policy and argued for both quantitative risk assessment and benefit-cost analysis.

In the 1980 benzene case the Supreme Court held that OSHA must determine that a cancer risk is "significant" before taking steps to reduce or eliminate the risk. Justice John Paul Stevens commented favorably on the developing discipline of quantitative risk assessment. Stevens also opined that a reasonable person might regard a lifetime risk of 1 in 1,000 as significant yet regard a risk of 1 in 1,000,000,000 as trivial. In 1981, Justice William Brennan wrote for a majority of the Court (including Stevens) rejecting the legitimacy of benefit-cost analysis under the Occupational Safety and Health Act. Since these two rulings, OSHA has embraced quantitative risk assessment and used 1 in 1,000 as a threshold of significant risk.

EPA's Range of Acceptable Risks

The creation of the Superfund program in 1980 spawned an explosion of risk assessments at abandoned waste sites across the country. In the Superfund program, excess cancer risk is estimated based on exposure to a hypothetical highly exposed individual living near a hazardous waste site. In the early years of the program, a range of acceptable risk from 1 in 10,000 to 1 in 10,000,000 was used informally by some Superfund managers. In the 1980's the 1 in 1,000,000 standard became more frequently used as a justification for no-action decisions and, in some circumstances, as a cleanup goal. This number was apparently borrowed from FDA, even though the size of the exposed populations are not comparable and the costs of compliance in the two cases are not comparable. More recently, the Superfund program has defined acceptable excess cancer risk as a range from 1 in 10,000 to 1 in 1,000,000, which provides managers flexibility to consider site-specific factors such as population density, feasibility, and cost-effectiveness.

The range-of-risk approach has also been adopted by other program offices within EPA. In setting guidance for state water quality standards, EPA recommends a range of acceptable risk from 1 in 100,000 to 1 in 10,000,000, although in recent years the agency has approved state plans with an implicit risk level as large as 1 in 10,000. Meanwhile, EPA's air office seeks to reduce risk to as many people as possible to 1 in 1,000,000 while assuring that the maximally exposed individual is protected against risks greater than 1 in 10,000. During deliberations over the 1990 Amendments to the Clean Air Act, Congress rejected a prominent proposal to shut down any industrial facility that could not comply with a cancer risk level of 1 in 10,000 and ultimately 1 in 1,000,000 for the maximally exposed individual. While Congress retained the 1-in-1,000,000 benchmark as a screening tool to guide EPA priorities in setting residual emission standards, Congress expressed a healthy skepticism about the scientific basis of current risk assessment practices. Congress called for a National Academy of Sciences study of EPA's risk assessment methods and a Commission on Risk Assessment and Management to recommend a new legislative framework.

Beyond Magical Risk Levels

Although some observers see value in "bright-line" levels of acceptable risk, history suggests that acceptable risk will ultimately be defined on a case-by-case basis. Key decision factors such as the size of the exposed population, the resource costs of meeting risk targets, and the scientific quality of risk assessments vary enormously from one decision context to another. Administrative discretion is necessary to weigh these factors on a case-by-case basis. No magic risk number can substitute for informed and thoughtful consideration by accountable officials who work with the public to make balanced decisions.

Further Reading
Alon Rosenthal, George M. Gray, and John D. Graham, "Legislating Acceptable Cancer Risk from Exposure to Toxic Chemicals," *Ecology Law Quarterly*, vol. 19, pp. 269–362, 1992.

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History

of the

U.S. Food and Drug Administration

Title:	**A Brief History of Risk Assessment**
Lecturer:	**Peter Barton Hutt, Esq.**
Date:	**November 1, 2000**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

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GENERAL TOPIC OF LECTURE: History of the Food and Drug Administration/A Brief History of Risk Assessment

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LECTURER

NAME: Peter Barton Hutt, Esq., FDA General Counsel

FDA SERVICE DATES: FROM: 1971 TO: 1975

LAST FDA POSITION HELD: FDA General Counsel

INDEX

A Brief History of Risk Assessment

Peter Barton Hutt, Esq., FDA General Counsel

November 1, 2000

TAPE 1, SIDE A

Good morning, everyone. I very much wish that I could be with us at the seminar this morning, but, unfortunately, I have a prior commitment on the West Coast, and thus this videotape appearance will have to substitute. But I am pleased that I can at least fill you in on some of the development of quantitative risk assessment over the past 30 years at the Food and Drug Administration.

But first you must understand that no regulatory policy simply springs full-blown from the head of a regulatory agency without prior history and prior development. And quantitative risk assessment is indeed one of the oldest concepts in human history.

If you go back in history, you find that for centuries, literally from the beginning of recorded history, every recorded civilization has regulated food and drugs one way or another, through laws, regulations, tradition, from biblical times, indeed from the clay tablets of ancient Sumaria to the present. And when you

try to regulate, one of the issues is, how do you define safety.

Let me give you, for example, one of my favorite statutes enacted by Parliament in 1266. The statute prohibited the addition of any substance to the then-staple food supply if that substance was -- and I give you a direct quote -- “not wholesome for man’s body.” Now, that is no different than our current definition of safety, but it provides no operational content. And thus from the beginning of time to today, the whole search in regulatory law is to provide good science that will in fact incorporate an operational definition of safety.

In those days, of course, in 1266 and, indeed, going back to early recorded history, how did we find what was safe? By having either wild animals or domesticated animals or even humans eat the substance. And if you think that’s far-fetched, and if you think that’s ancient history, let me give you just something that happened a hundred years ago.

In 1902 to 1904, the famous FDA Commissioner, Dr. Harvey W. Wiley, wanted to publicize the issue of food safety, and he chose a way to do that that I’m sure you are all going to be somewhat amused by. What he did was find the 10 youngest members of the then Center -- it really

wasn’t a Center, it was a Division of Chemistry in the United States Department of Agriculture, and he took the five leading food preservatives of that time and fed them to those people for two years, a human feeding experiment. There was no concept of animal testing in those days. And to further illustrate just how remarkable this was, one of those preservatives was formaldehyde. So we have, just a hundred years ago, a human feeding study in formaldehyde. That was the way because there was no operational definition of safety that things were determined either to be harmful or to be safe in those days, not that long ago.

Now, things began to change very rapidly. For reasons that are lost in history, suddenly scientists, academic scientists, throughout the country began to develop inbred colonies of test animals. By 1920, animal testing had suddenly come into vogue, and it was, some people hypothesize, largely a rediscovery of Mendel’s laws of heredity that resulted in this scientific progress. But we begin to see in 1920, and going on up through the decades, increased reliance in our country and throughout the world on use of animal testing experiments to determine safety. But the issue remained, what was the definition, the operational definition, of safety that came out of those experiments?

In the 1930s, people began to think about an operational definition, and indeed, there's a wonderful paper in 1935 by Dr. Berenblum in which he began to focus on the issue of chemical potency. And, of course, everyone knew at that time, that has often been said, that dose makes the poison, but no one knew where to draw the line between a poison and a safe dose. Berenblum was the first person in the area of carcinogenicity that I have been able to find who attacked that on a mathematical basis and tried to resolve it.

But then came along, as it often does in history, a remarkable event no one could have predicted that suddenly began to focus people on the real issue of operational definitions of safety.

In the fall of 1937, a well-known pharmaceutical company of that era, still with us today, Massengill, brought out what today we would call a breakthrough drug, elixir sulfanilamide. The scientific progress that this represented was that sulfa had never before been put into solution, and Massengill solved that problem. They did some chemical testing, no animal testing, rushed this product out into the market, and managed to kill 120 people in two days, because the solvent they used was diethylene glycol. Now, of course, this led to not only a nationwide

recall, but it also led to the enactment of our current Federal Food, Drug and Cosmetic Act of 1938.he was involved in.

But there were two brilliant and really thoughtful FDA scientists who said, “Let’s learn from this. How often do you have this kind of a tragedy that you can turn into a real benefit to public health?” And so Dr. H.O. Calvary and Dr. Hogarth Fitzhugh, FDA toxicologists, both went out and did a remarkable set of experiments. The first thing they did was they collected all the information on the people who had taken elixir sulfanilamide, the dose they had taken, the amount of time they had taken it, and their body weight, and then they figured out who lived and who died.

Following that -- and you can imagine, that’s obtaining an LD50, a human LD50 for elixir sulfanilamide.

Then what they did was go back and do the animal experiments that Massengill should have done. They did them in a wide variety of species: rats and mice and hamsters and dogs, and everything else. And what they discovered was that there was roughly a tenfold variation among humans and roughly a tenfold variation among the animals. They multiplied 10 times 10, arrived at 100, of

course, and therein lies the history of the famous FDA 100-to-1 safety factor.

You will be interested to know that I have never seen this written up. Someday I am going to write up this story.

I interviewed Hogarth Fitzhugh before he died, as well as all the other then-living FDA toxicologists of that era, and discovered that this was one of the great unknown heroic stories of the Food and Drug Administration of that era.

Well, you might say, okay, we have a 100-to-1 safety factor for acute toxicity. What about chronic toxicity? And, more important, what about carcinogenicity?

Fitzhugh told me that all of the folklore I had learned, that the 100-to-1 safety factor had initially been applied to carcinogens, then they had increased it to 2,000-to-1, and then 5,000-to-1, was all nonsense. It was untrue. FDA never once applied a safety factor to a carcinogen. And, in fact, I went back and discovered, as early as 1945, FDA banned its first carcinogen, a substance called butter yellow. In 1950, FDA banned two non-nutritive sweeteners. You probably have never heard of them before: dulcin and P4000. And, thus, long before Mr. Delaney invented his famous Delaney Anti-Cancer Clause and

put it in the Federal Food, Drug and Cosmetic Act of 1958, FDA had adopted a policy of zero tolerance, no permitted amount of carcinogen in any food in the United States could be had.

Now, this was, of course, incorporated into the law. But the Delaney Clause, I have always thought, was misunderstood. The Delaney Clause does not say that Congress knew that one molecule of any carcinogen would cause human cancer. What the Delaney Clause said was basically the same thing that Fitzhugh and Calvary and the others were saying much earlier, 15 years earlier, and that is, we don't know how much of a substance is needed. We don't know how potency plays in the area of carcinogenicity. And, therefore, we will, until we learn more, adopt a policy. We won't add carcinogens to the food supply. It was a principle of conservatism. It was not based on scientific knowledge; it was based on the lack of scientific knowledge.

Now, only four years after the Delaney Clause was enacted as part of the Food Additives Amendment of 1958, Congress was presented, surprisingly, with quite a different issue, and one that, for our purposes this morning, is very important. Congress had to face this. Part of the food-additives definition excludes from the

definition of food additive any substance that had been approved by FDA or USDA prior to 1958. Included in those substances was a well-known chemical, you all know it very well, diethylstilbestrol, or DES. And what happened was that the largest manufacturer of DES in the country had a prior sanction for that substance. His plant burned down. He built another plant across the street to make the same substance, and FDA took the position that he couldn't make it because the prior sanction only applied to the first plant and did not apply to the second plant. So, surprisingly, Congress enacted a law as an exception to the Delaney Clause, saying that FDA could approve a carcinogenic animal drug if in fact the residues of that animal drug were not found in the food produced by the animal using methods of analysis approved by the Food and Drug Administration. That basically is what that amendment stated. And, as we will see in one moment, it was that amendment that led to the development of quantitative risk assessment as a regulatory tool in this country.

Now, FDA, faced in 1962 with this amendment, had to come up with a definition of what method of analysis is approved, and what they did was they came up with a mouse uterine acid sensitive to two parts per billion. So from 1962 to 1972, FDA allowed DES to be used, to be made and to

be used in food-producing animals, both in the feed and in implants, based on the mouse uterine acid.

Well, in 1971, unfortunately, just at the time that I arrived at FDA as Chief Counsel, things began to change, and ominous clouds gathered over this entire enterprise. There were three congressional hearings in 1971 questioning FDA's policy on DES. And USDA decided they would definitively resolve this matter. They later, I might add, regretted that decision very much.

So in early 1972, USDA undertook a study in which they tagged, did radioactive tagging of DES to find out exactly what happened to it in the food, in the cattle that it was used in. And, not surprising -- I'll never forget it -- July 28th, 1972, I got a telephone call that in effect said, "Not only have we found it, we found it everywhere. We know exactly where the DES is going. It doesn't get out of the animal. It's still there, at very low levels, but it's there." I spent the next three days writing a *Federal Register* notice that banned DES from animal feed, and a year later, of course, we did the same thing with implants.

Now, it was one thing to lose DES. The Secretary of Agriculture informed me I had just raised the price of beef seven cents. I must admit, that did not concern me. What did concern me was, we had been approving carcinogenic

animal drugs for 10 years based on this concept of what I came to call, to the consternation of scientists throughout the country, hide-and-go-seek toxicology, i.e., if you can't find it, it isn't there. We all know that's not true. If you can't find it, it's because you don't have good enough analytical methods to find it. That is true.

So I said to the Center for Veterinary Medicine, I sent them a memorandum shortly after the DES controversy abated, and I said, "I will approve no more animal drugs that are carcinogenic based on the old policy. We must come up with a new policy that is both legally and scientifically sound."

Now, you might say, "Well, who cares what the General Counsel says about animal drugs?" The answer was, since they all, all the approvals had to be published in the *Federal Register*, they could only get there if I approved them. And since I declined to approve them, there was a growing stack on the right-hand side of my desk of *Federal Register* notices that, as far as I was concerned, would never see the light of day unless and until we came up with a new method of approaching this. So there was, in a sense, a mounting crisis both in the Bureau of Veterinary Medicine as well as in my own mind.

During this entire time, during this saga of DES, things were going on that, frankly, I had no knowledge about, both in the Center of Veterinary Medicine as well as in academia. People had been trying to confront, on a purely academic level, this issue that Berenblum had started with in 1935. And this culminated in the National Institutes of Health (NIH) in two well-known and well-respected scientists, Mantel and Bryan, coming up in 1961 with a concept that not only quantified carcinogenic risk, but purported to determine what was, in their terms, a virtually safe dose. And they did it by a mathematical model, but they chose as the virtually safe dose a, if you will, safety factor of no greater than 1-in-10-billion risk, 10^{-8}. That was in the scientific literature for 10 years. And, of course, because it was an academic issue, no one in FDA paid any attention to it at all, except for one person, Adrian Gross, an FDA toxicologist.

Now, Adrian Gross at that time was at FDA. Later -- in fact, he was in the Bureau of Veterinary Medicine. Later, he went to the Environmental Protection Agency (EPA). EPA. He was a difficult person. He was personally not the easiest individual in the world to get along with. He was highly persistent, he was a very, very strong consumer advocate, but he was also a very intelligent and

thoughtful person. And as early as 1970, Adrian had published an article applying the Mantel-Bryan, not to a carcinogen, to a chemical that he thought, erroneously as it turned out, was a reproductive toxicant, the flavoring substance methyl salicylate.

Well, Adrian, in 1971, internally in the Center, or then, as it was, Bureau of Veterinary Medicine, began to write memoranda that I discovered literally 10 years later by reading congressional hearings, stating that Mantel-Bryan ought to be used on substances like DES. Those internal memoranda never got out of the Bureau, never got to me, never got to the Commissioner's office, and, thus, we were unaware of it.

But when those applications began to pile up on my desk, one afternoon a very, very fine, bright, extraordinary scientist from the Bureau of Veterinary Medicine walked into my office, his name Dick Layman [sp.] -- he's retired from FDA now -- and he sat down and said, "Peter, I've got to talk to you. Here is a possible way to solve this problem." In less than a half hour, Dick laid out to me the concept of Mantel-Bryan, the concept of a quantified risk, and the solution to the problem. It took me probably five minutes to realize this was in fact the solution, not a perfect solution, but this was the only way

to go, to quantify risk and then determine what level of risk is acceptable to our society.

That night I called Charlie Edwards, the Commissioner of FDA, and said, “Charlie, this is the way to go.”

And Charlie, being the person he was, said, “We go with it.” That decision was made in a matter of minutes.

Nonetheless, it took more than a year to draft this up for purposes of the *Federal Register*.

You’ll be amused to know that almost everybody in FDA found objections to it. Now, why was that? Well, the Bureau of Foods opposed it because Leo Friedman, the great toxicologist that he was, and Al Copey [sp.] both said, “We want to rely on scientific judgment. We don’t want to be hemmed in by rules and mathematical formula and specific levels of acceptable risk. Charlie and I simply said, “You can’t go that way.”

Then the Bureau of Veterinary Medicine weighed in, Dr. Van Houweling and others there, who said, “We can’t meet this standard of 10^{-8}. That would mean that almost all of these carcinogenic animal drugs would not survive.”

Now, let me explain exactly why they were concerned. The way that Mantel-Bryan was proposed to be used was as follows: What you did was calculate the amount of residue in the food that would be permitted in order to assure only

a 10^{-8} risk, and then you require the applicant to come up with a method of analysis sensitive to that level that represented 10^{-8}. Once you did that, and then you showed no residue at that level, it was approvable.

Now, Van Houweling kept saying to me -- and we came to call this the Sensitivity of the Method proposal -- that the SOM proposal was unworkable. Simply, it was a lovely academic idea, but, in fact, what it would do is ban everything. Well, we now know that it hasn't banned everything. It is still the policy that is pursued by FDA today in approving carcinogenic animal drugs.

Now, events that we could not have foreseen way back in 1972, when I was dealing with this, have now made this policy, the concept of using quantitative risk assessment, far more effaceable an any of us ever could have imagined.

As you know, and as we all know now, almost 30 years later, many, many more chemicals have been tested and, for example, in the National Toxicology program (NTP) NTP program, 50 percent of the tested chemicals have turned out to be carcinogenic. The improvements in analytical methodology means that we can find these substances everywhere, absolutely everywhere. As early as 1979, FDA actually published a statement in the *Federal Register* saying that, in fact, every bit of food in the country

contains some carcinogen of one form or another. We could not live without eating substances that have been tested and found to be carcinogenic in test animals. And thus, the old policy that Olgarth Fitzhugh followed in 1945 and thereabouts of banning every carcinogen, we can't do, and we haven't been able to do it for 30 years.

Thus, as it turns out -- and none of us, I can tell you, certainly not me, and I drafted much of it, none of us at the time anticipated it would become as pervasive in the entire government and as important to FDA as it, in fact, has become.

There are a couple of other principles we developed at the same time. One of them is that we realized that not everything that came up carcinogenic in a test animals was in fact appropriately designated a carcinogen. And we began to take into account whether in fact the animal was a good model for the human. And these are well-known examples. The most amusing to me is, if you feed calcium to bulls, they get cancer. That has never driven FDA to ban or restrict calcium in our diet. As you well know, BHA and BHT are suspect carcinogens, but FDA has done nothing because they have concluded that the animal model is not a useful model for the human.

A second area where FDA has taken action is to recognize that some carcinogens act through a secondary rather than a primary method. And, in fact, I wrote the regulations back in the 1970s that said that FDA would not ban alcoholic beverages -- that was an easy one; I had little doubt about that one -- or selenium because they were carcinogens, indeed, human carcinogens, but they acted through a secondary mechanism of action and thus were not under the Delaney Clause.

And, finally, we realized, though, that those ways of getting substances out from under Delaney were [unclear]. The basic mechanism, the basic policy that we had to rely on, had to do with quantitative risk assessment.

What we then saw was the proliferation of quantitative risk assessment throughout the entire food and drug area. For example, the hair dyes 4-MMPD and lead acetate were approved by FDA based on quantitative risk assessment. Food contaminants like aflatoxin and dioxin were approved, or not approved but at least permitted based on quantitative risk assessment. Acrylonitrile and vinyl chloride was recognized to be permitted in food packaging based on these principles, and, of course, other food constituents.

FDA had to go in through this piecemeal, finally came to a food-constituents policy, which states that if there is a constituent in food that is carcinogenic -- and there are hundreds of them -- they are not required to be banned as long as they do not present a significant carcinogenic risk.

The final part of this is, what is an acceptable level of safety? Now, Mantel and Bryan started at 10^{-8}, 1 in 10 million, and -- I'm sorry, 1 in 100 million. And after considering that and listening to both the industry and to the scientists in FDA, the final regulation on sensitivity of the method and the level chosen by FDA ever since there was reduced to 1 in a million, so that this is a much more realistic risk.

Now, FDA has not only reduced it to 1 in a million, but FDA has flatly said, in probably 50 different *Federal Register* notices, that the 1-in-a-million risk, 10^{-6}, means no carcinogenic risk at all, that while that is a mathematical possibility, it is not a real risk in the actual practical world. Moreover, my feeling is that, in the future, there are possibilities for reducing that. Under Proposition 65, for example, California has gone to 1 in 100,000.

Now, where can we reduce that? We can reduce that with better science. If we can understand better the pathways, the mechanism of action of some of these carcinogens, we can understand how animal and humans are either the same or different in particular chemicals or for classes of chemicals. We will be able to have greater confidence in extrapolation from high dose to low dose, and therefore will be able to reduce the 1 in a million not only down to 1 in 100,000, but in some chemicals, much lower than that. I don't know if we'll ever get to the same level that we started with Calvary and Fitzhugh of 100 to 1 for acute risk, but certainly we will get below 1 in a million.

What we need most of all in this area is public education. The public doesn't understand this at all. They hear the word cancer or carcinogen and they freak out. I don't blame them. It's a frightening thought. We need to educate people about risk assessment. We need to educate them about the enormous amount of conservatism built into our present system.

There are still consumer activists out there who want to ban every single carcinogen that exists. Fortunately, FDA has never felt that way, they know it's not possible, and they are willing to rely on good science.

Well, I simply want to close by saying it’s been a pleasure this morning to be able to be with you, even if by videotape. I hope this bit of history is of interest to you and that it will, in a sense, pave the way for the real experts, the scientists, my good friends from Environ, who are going to go into the details of quantitative risk assessment in just a few minutes.

Thank you very much for being with me and for allowing me to be with you.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 27]

QUALITY STANDARD FOR CANNED CHERRIES

Proposed Revision of Blemish Limitation

Notice is given that a petition has been filed by the National Canners Association, 1133 20th St., NW., Washington, DC 20036, proposing that the standard of quality for canned cherries (21 CFR 27.31) be amended by:

(1) Changing the definition of a blemished cherry; and

(2) Increasing the aggregate area of the blemish from $\frac{1}{16}$ inch to $\frac{9}{32}$ inch in diameter.

Grounds set forth in the petition in support of the proposal are that: (1) The proposed change in the definition of a blemished unit would be consistent with objections received to an order, published in the FEDERAL REGISTER on February 23, 1971 (36 FR 3364) ruling on a proposed cherry pie standard of quality (21 CFR 28.2). These objections requested that the $\frac{1}{16}$ inch diameter limit for blemished units be changed to a $\frac{9}{32}$ inch diameter limit. The Commissioner of Food and Drugs granted this request in the FEDERAL REGISTER of June 13, 1973 (38 FR 15503).

(2) Mechanical harvesting and bulk handling in tanks of water have replaced the traditional hand picking and handling. As a result there has been a greatly increased problem with a mild form of discoloration known as "tank or water scald" which results in minor color variation but does not affect the tissues or eating quality or the cherries.

(3) Since the present standard was established 32 years ago, changes in cultural practices have resulted in the production of larger and softer cherries. Presently, there are as few as 100 to 110 cherries per pound as compared to 140 to 150 per pound when the standard was adopted. The larger, softer cherries have aggravated the blemish problem because they are more susceptible to blemishes and contain a greater surface area compared to the permitted area of skin discoloration.

(4) Increasing the area of the blemish to 9/32 inch would bring the quality standard for canned cherries (21 CFR 27.31) into agreement with the present voluntary U.S. Department of Agriculture standard for grades of frozen cherries.

(5) The proposed change will insure consumers a continued supply of canned cherries without significantly affecting the quality.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 701, 52 Stat. 1046, 1055 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 341, 371) and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Part 27 be amended in § 27.31 by revising paragraph (a)(5) to read as follows:

§ 27.31 Canned cherries; quality; label statement of substandard quality.

(a) * * *

(5) Not more than 15 percent by count of the cherries in the container are blemished with scab, hail injury, discoloration, scar tissue or other abnormality. A cherry showing skin discoloration (other than scald) having an aggregate area exceeding that of a circle 9/32 inch in diameter is considered to be blemished. A cherry showing discoloration of any area but extending into the fruit tissue is also considered to be blemished.

* * * * *

Interested persons may, on or before September 17, 1973 file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: June 20, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-14749 Filed 7-18-73;8:45 am]

[21 CFR Part 135]

COMPOUNDS USED IN FOOD-PRODUCING ANIMALS

Procedures for Determining Acceptability of Assay Methods Used for Assuring the Absence of Residues in Edible Products of Such Animals

The Federal Food, Drug, and Cosmetic Act requires that compounds administered to animals as food additives, color additives, or animal drugs be shown to be safe for use. The term "safe" refers to the health of man or animal under section 201(u) of the act. In evaluating the safety of such compounds used in food-producing animals, consideration must be given to the safety of possible residues in the products of those animals which are a source of food for man. When there is insufficient evidence to establish that a finite or negligible residue of the compound is safe in human food, or when the anticancer clauses contained in sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B) of the act are applicable, a zero tolerance (no residue) must be required. (Under the provisions of the anticancer clauses no compound may be administered to animals which are raised for food production if such compound has been shown to induce cancer when ingested by man or animal, unless such compound will not adversely affect the animal and no residues, as determined by methods of analysis prescribed or approved by the Secretary, are found in the edible products of such animals under conditions of use specified in labeling and reasonably certain to be followed in practice. A decision is then required as to whether a practicable method exists to determine the absence of such residues in food, under sections 409(b)(2)(D), 512(b)(7), and 706(b)(5)(A)(iv) of the act.

The Commissioner of Food and Drugs has determined that it would be in the public interest to set forth the principles involved in application of these safety provisions of the law with respect to the adequacy of the sensitivity of the required regulatory assay method for monitoring compounds which may be administered to food-producing animals, but for which no residue is permitted in human food. Therefore, a new regulation is proposed to establish the minimum standards for determining the acceptability of assay methods used to assure the absence of residues in edible products of such animals. These proposed regulations do not apply to drugs for which a finite or negligible residue is established as safe for human food.

The proposed new regulation will apply to two classes of compounds administered to food-producing animals: (1) Exogenous compounds, defined as those compounds which are not produced by the normal animal and are not required for normal animal body function (e.g., diethylstilbestrol), and (2) Endogenous compounds, defined as those compounds which are present in and produced by the normal animal and are not required from an exogenous source (e.g., estradiol).

In evaluation of the safety of compounds of both classes the initial testing must involve detailed metabolism studies in the target species. Radiotracer studies are usually the method of choice. The purpose of these studies will be to identify the metabolites of the compound, both qualitatively and quantitatively, and the concentrations of the compound and its metabolites in specific tissues ("tissues" include milk and eggs, if applicable). Another aspect of these studies will be the determination of the effect of the administration of the compound on tissue levels of related endogenous compounds.

For acceptable studies, it is necessary to follow the degradation of the compound and/or its metabolites after slaughter and during the period that the edible tissue would normally be held under storage conditions as well as to determine the impact of cooking at appropriate temperatures on the compounds in question.

EXOGENOUS COMPOUNDS

Determination as to whether an exogenous compound and/or its metabolites will require carcinogenicity testing will be based on the results of the metabolism studies, standard toxicity testing, structural relationships of the compound and or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended use pattern of the compound. Tests for carcinogenicity will be routinely required for any new compound for which a priori knowledge is incomplete and which is intended to be used for disease prophylaxis and, or production purposes (e.g., increased rate of weight gain, estrus synchronization, etc.).

01133

If it is determined that tests for carcinogenicity are not required, or if the results of such tests are negative, consideration leading to approval will be based on standard toxicological procedures. These procedures will include, in addition to subacute studies in a minimum of two species, such studies as multi-generation reproduction studies, teratological and any other special studies which may be indicated from the nature of the biological action of the compound, including life-time studies. These studies will involve collecting data from appropriately designed dose-response experiments that demonstrate a maximum "no harmful effect level" as well as a minimum "harmful effect level" in appropriate animal species.

Where a residue is permitted as safe in human food (either as a finite tolerance level or as a negligible residue of less than a specified level), the sensitivity of the assay method will be required to meet the specified level, and the other provisions of this proposed new regulation relating to the required sensitivity of the method will be inapplicable. Where no residue (zero tolerance) is permitted, the provisions of this proposed new regulation are fully applicable.

Under the proposed new regulation the dose-response slope estimated from the toxicological experiments will be used to extrapolate to the required level of sensitivity of the method using appropriate confidence interval techniques in accordance with the concepts underlying the Mantel-Bryan procedure discussed below. Where such extrapolation is not scientifically appropriate, e.g., if no dose-response slope can be estimated from the data, other conservative methods will be invoked to determine an appropriate safety margin based on a thorough evaluation of the quality of the experiments, their rigor as predictive tests and the nature and significance of the observed biological effects.

Where tests for carcinogenicity are required for a compound there are two basic objectives of the tests. The first is to determine whether or not the compound and/or its metabolites is a carcinogen. The second is to determine the relative potency of the compound and/or its metabolites with respect to both its carcinogenic and its noncarcinogenic but toxic effects, through appropriate oral dose-response experiments. Test systems will be selected which maximize sensitivity to detect a minimal dose which induces a carcinogenic effect. These systems will include a sufficiently stable control population to avoid false-positive indications of carcinogenesis.

There is a general lack of agreement within the scientific community regarding appropriate protocols for determining the dose-response relationship of carcinogenic compounds. Until they are revised, the guidelines for protocols set out by the Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides (Toxicology and Applied Pharmacology Vol. 20, pp 419–438, 1971) will be followed by the Food and Drug Administration.

If the results of the test for carcinogenicity establish that the compound or its metabolites will induce cancer in test animals, the required sensitivity of the regulatory assay method will be determined based on the Mantel-Bryan procedure described in the article entitled "Safety" Testing of Carcinogenic Agents (Journal of the National Cancer Institute, Vol. 27, pp 455–470, 1961). However, rather than assuming a dose-response relationship with a slope of one, as suggested in the reference, experimental data obtained from the carcinogenicity studies will be used to obtain a statistical estimate of the slope of the dose-response relationship. The lower 90 percent confidence limit of the estimated slope will be used for extrapolation to the required level of sensitivity of the regulatory assay method. If the data indicate that some linearizing transformation other than the probit-log transformation used in the modified Mantel-Bryan procedure better describes the observed response and has a biological rationale, then this other linearizing transformation may be used for such extrapolation. Examples of the application of this technique are given in the above reference.

Absolute safety can never be conclusively demonstrated experimentally. The level defined by the Mantel-Bryan procedure is an arbitrary but conservative level of maximum exposure resulting in a minimal probability of risk to an individual (e.g., 1/100,000,000), under those exposure conditions of the basic animal studies. Such test conditions generally involve continuous daily lifetime exposure to the compound in question. In contrast, many types of foods are consumed only intermittently, e.g., turkey or broiler kidneys, and therefore any drug residues contained in such foods will be consumed only intermittently. If the same procedure was used to determine the level of exposure for turkey kidneys as was used to determine the level of exposure for foods consumed more frequently, such as beef muscle, the population would not be equally protected in both situations. Consequently, it will be necessary to adjust the procedure for establishing the exposure level to account for usual as well as specific human consumption patterns. Any such adjustments initially will be made on a conservative basis. These adjustments will take into consideration the consumption expected by those who consume the greatest amounts of food, not the average consumption of the food. More definitive information is being complied on food consumption patterns by the Food and Drug Administration, and this information will be used to arrive at more refined adjustments as it becomes available.

It will also be necessary to modify the procedure for establishing the exposure level to account for drug usage, patterns, e.g., the administration of a drug in the treatment of diseased animals. As with consumption patterns, justified modifications will be made on a conservative basis. If a disease has a maximum incidence of 10 percent, then no more than 10 percent of the marketed animals would have been treated with the drug. Under these conditions, the probability of continuous daily exposure for an individual consumer could be very conservatively estimated as 0.10. In this situation, the true probability of risk for the individual consumer would then equal the probability of individual risk under conditions of continuous daily exposure to the drug multiplied by the probability of an individual actually experiencing continuous daily exposure to the drug. If a true exposure of 1/100,000,000 were deemed acceptable for an individual on the basis of risk-benefit considerations, this value could be held constant by assuming a continuous exposure risk of 1/10,000,000 (1/100,000,000=1/10,000,000 X 0.10) in the estimate of the Mantel-Bryan level. The true individual consumer risk would remain at 1/100,000,000 since the consumer is only intermittently exposed to residues of the compound in food.

The maximum level of exposure as estimated above, after standard adjustment for the differences between daily food intake per unit of body weight of the laboratory animal as compared with man, will be the required sensitivity of the assay method for a compound. In the event that both non-carcinogenic harmful effects and carcinogenic effects are observed during testing, the lowest level for the regulatory assay sensitivity as determined for the different effects will be adopted.

Withdrawal or post-medication periods for exogenous compounds shall be based on data obtained from tissue depletion studies. The compound must be administered to test animals for a sufficient time for concentration equilibrium to be achieved. On the basis of the developed assay and/or other suitable methods, a determination must be made as to the time when tissue levels of the parent compound and/or its metabolites and/or any affected endogenous compounds are below the required level of sensitivity for the regulatory assay method.

The withdrawal period shall be the longer of: (1) The number of days for tissue levels to be depleted to less than the maximum level of exposure extrapolated by the modified Mantel-Bryan procedure plus a safety factor to account for animal to animal variation (as determined by appropriate confidence interval techniques) or (2) the number of days for any affected endogenous compound to return to normal levels plus a safety factor to account for animal to animal variation. (The normal level of the affected endogenous compound will be established as described below for endogenous compounds.) For example, if excretion data indicate that the average depletion time for an exogenous compound is 72 hours with a safety factor of 27 hours, the withdrawal period becomes (72 hours+27 hours) = 24 hours or, after

01134

rounding upward, 5 days. Current livestock management techniques must be considered in establishing the withdrawal period and may necessitate the lengthening of this period.

The provisions of the proposed new regulation govern the required level of sensitivity of the regulatory assay method for those compounds for which a zero tolerance (no residue) is established. If a regulatory assay method of lower sensitivity is later developed and validated, however, the Commissioner will adopt that more sensitive method and publish it in the FEDERAL REGISTER, even though its development was not required under the law.

ENDOGENOUS COMPOUNDS

It is proposed that animals shown to contain tissue levels of endogenous compounds above the normal due to the administration of such compounds will not be permitted to be marketed for human consumption. Thus, neither tests for carcinogenicity nor standard toxicity testing will be required for endogenous compounds.

Naturally occurring (background) tissue levels of endogenous compounds and/or their metabolites and/or other related endogenous compounds in the target species must be determined in studies designed to show the effect of geographical location, stage of estrus, age, etc., on normal animals receiving no external source of the endogenous compound. The tissue distribution of the levels of the compound and/or its metabolites and/or other related endogenous compounds will be estimated from these studies. This distribution will be used to establish the required sensitivity of the regulatory assay method. The required sensitivity will be that level of the tissue distribution which is exceeded by only one percent of the normal animals. Tissue samples from animals at slaughter will be considered suspect if a level is found above normal background. For example, if 99.0 percent of background tissue levels for a parent endogenous compound and/or its metabolites and/or other related endogenous compounds are below 16 ppt., then a tissue level greater than 16 ppt shall be considered suspect. The final determination with respect to regulatory action will be based on a field investigation to determine if the observed value was due to a misuse of the compound or if it was due to normal biological variability.

Withdrawal periods following the last dosage for endogenous compounds shall be established based on the time required for the level of the parent compound and/or its metabolites and/or other related endogenous compounds in the tissue to return to the median background level of contemporary controls. The maximum approvable level of the compound shall be administered to target animals for a period of time sufficient to establish equilibrium in tissues. The number of days required for tissue levels of any affected endogenous compounds to return to the median background level plus a safety factor to account for animal to animal variation (as determined by appropriate confidence interval techniques) shall be used to establish the required withdrawal period. Current livestock management techniques must be considered in establishing the withdrawal period and may necessitate the lengthening of this period.

ASSAY EVALUATION CRITERIA

Prior to approval, the accuracy and reliability of the regulatory assay must be determined by validation of the method in appropriate Food and Drug Administration laboratories and other laboratories. The objectives of the validation will be to determine the feasibility, specificity, accuracy, and precision of the method (including a determination of the amounts recovered as well as an estimation of the variation associated with the recovered amounts).

Prior to submission of a method for evaluation and subsequent validation, it is recommended that the method be reviewed and tested, both qualitatively and quantitatively, by independent laboratories. This evaluation should fulfill the objectives of the validation as listed above.

The required sensitivity of the regulatory assay method as previously defined will be the regulatory action level and will be published in the FEDERAL REGISTER. Since any "positive" finding reported at a level lower than the published level of sensitivity may actually be a false positive, regulatory action will be taken only at or above the published level. This is necessary in order to assure that a residue is in fact a true positive. In the past the lack of such a procedure has led to finding violative samples in one laboratory which could not be confirmed in a second laboratory.

The assay method will be published or referenced in the FEDERAL REGISTER and will include a definition of the response criteria unique for each method which represents a reliable positive finding based on the validation studies. The criteria will take into account adjustments based on the accuracy and precision of the method. If the method is not specific for the identification of the compound or there are reasons to suspect the occurrence of false positives due to interference, a practical confirmatory test must be provided which will identify the residue at the level of sensitivity required.

In summary, the development and validation of a regulatory assay method for monitoring purposes must consider the following criteria:

1. The method must be capable of reproducibly extracting, at the required level of sensitivity, the significant compounds from target tissues obtained from treated animals as well as from tissues containing known added amounts of the compounds.

2. The method must be capable of measuring residues with a sufficient degree of specificity, precision, and accuracy to preclude the occurrence of false negatives or false positives.

3. The equipment, reagents and compounds used in the assay must be commercially available. Any required specialization in terms of equipment or personnel must be consistent with that normally available in a modern well-equipped analytical control laboratory.

4. The time required for completion of the assay must not be so excessive as to delay regulatory action, when necessary.

5. The assay must offer minimal hazard in the laboratory.

It is proposed that the requirements contained in this regulation will be applicable to all NADA's and supplemental NADA's approved by the Food and Drug Administration after the effective date of the new regulation. In determining the applicability of the provisions of the regulation to already-existing new animal drug approvals, the Commissioner will first determine those drugs for which a zero residue requirement now exists but for which a finite or negligible residue should instead be permitted. The Commissioner recognizes that many of these zero tolerances were established several years ago, at a time when detection methodology was substantially less sensitive and the available toxicology information was not as extensive. For some of these zero tolerances, it may now be possible and consistent with protection of the public health, to establish a finite or negligible residue. Where a finite or negligible residue is established on the basis of adequate safety data, the provisions of the new regulation will not be applicable.

Where a zero tolerance is deemed necessary, either because of a determination of carcinogenicity or because the compound is a suspect carcinogen or is otherwise sufficiently toxic that a determination of a safe level of residue in human food cannot be made at this time, the provisions of the new regulation will be applicable. The Commissioner recognizes that these new requirements cannot be imposed immediately. Accordingly, a determination will be made with respect to each drug as to a reasonable amount of time within which compliance will be permitted. In those instances in which the Commissioner concludes that a health hazard may exist, or where there is a failure to undertake the requisitie studies, the Commissioner will proceed immediately to withdraw approval of the drug. Hence, the above approach will permit a reasonable transition to the new requirements without compromising the public health or disrupting the use of drugs for which there is no known health hazard.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 402, 403, 409, 512, 701(a), 706, 52 Stat. 1046–1048, 1055, 72 Stat. 1785–1788 as amended, 74 Stat. 399–404, 82 Stat. 343–351; U.S.C. 342, 343, 348, 706, 360b, 371(a), 376), and under authority delegated to the Commissioner (21 CFR

01135

2.120), it is proposed that Part 135 be amended by adding the following new section:

§ 135.38 Compounds used in food-producing animals; procedures for determining the acceptability of assay methods used for assuring the absence of residues in edible products of such animals.

(a) The act provides that feed and drugs intended for animals shall be safe, that food produced from animals shall be safe, and that any compound administered to a food-producing animal which is found to induce cancer when ingested by man or animal is prohibited from the food supply, unless it can be determined by methods of examination prescribed or approved by the Secretary by regulation, that no residues of any such compound are found in the food produced from such animals under conditions of use reasonably certain to be followed in practice. Petitions for use of a compound in food-producing animals shall include data for determining the absence of residues of any unsafe compounds in the food produced from such animals. The provisions of this section shall determine the required level of sensitivity of the regulatory assay method for any compound for which the Commissioner of Food and Drugs has established a zero tolerance (no residue) in food.

(b) Exogenous compounds, defined as those compounds which are not produced by the normal animal and are not required for normal animal body function, are subject to the following requirements:

(1) Metabolism studies shall be conducted in the target species to identify and quantify metabolites of the parent compound and the concentrations of the compound and its metabolites in specific tissues ("tissues" to include milk and eggs, if applicable). The effect of the exogenous compound on tissue levels of related endogenous compounds also shall be determined.

(2) Degradation of the compound and/or its metabolites during the period of time after slaughter that edible tissue would normally be held under storage conditions and the impact of cooking on the compound and/or its metabolites in question shall be determined.

(3) Determination of whether an exogenous compound and/or its metabolites shall be subjected to appropriate testing for carcinogenicity will be based on the results of the metabolism studies, standard toxicity testing, structural relationships of the compound and/or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended use patterns of the compounds.

(4) If it is determined that carcinogenicity tests are not required or if the results of carcinogenic testing are negative, consideration for approval shall be based on standard toxicological procedures. These procedures shall include in addition to subacute studies in a minimum of two species, such studies as a multi-generation reproduction studies, teratology and any other special studies which may be indicated from the nature of the biological action of the compound, including lifetime studies. These studies shall involve collection of data from appropriately designed dose-response experiments that demonstrate a "maximum no harmful effect level" as well as a "minimum harmful effect level" in appropriate animal species.

(i) Where a finite or negligible residue of the parent compound and/or its metabolites is determined to be safe in food, the required level of sensitivity of the regulatory assay method will be the level of the tolerance published in the FEDERAL REGISTER and the remaining provisions of this paragraph shall be inapplicable.

(ii) Where no residue of the compound and/or its metabolites is determined to be safe in food, the dose-response slope estimated from the toxicological experiments will be used to extrapolate to the required level of sensitivity of the method using appropriate confidence interval techniques in accordance with the concepts underlying the Mantel-Bryan procedure described in paragraph (b) (6) of this section. Where such extrapolation is not scientifically appropriate, e.g., if no dose-response slope can be estimated from the data, other conservative methods shall be invoked to determine an appropriate safety margin based on a thorough evaluation of the quality of the experiments, their rigor as predictive tests and the nature and significance of the observed biological effects.

(5) If it is determined that testing for carcinogenicity is required, test procedures shall be used which maximize sensitivity to detect a minimal dose which induces a carcinogenic effect and with a sufficiently stable control population to avoid false positive indications of carcinogenesis. Appropriate dose-response experiments shall be conducted to (i) clearly establish whether or not the compound and/or its metabolites are carcinogens, and (ii) determine the relative potency of the compound and/or its metabolites with respect to both its carcinogenic and its other toxic effects.

(6) If it is determined that the compound is carcinogenic, the required sensitivity of the regulatory assay method shall be established according to a modification of the Mantel-Bryan procedure. (Mantel, N. and W. R. Bryan, "Safety" Testing of Carcinogenic Agents, Journal of the National Cancer Institute, Vol. 27, pp. 455–470, 1961).[1] This modification shall consist of using the lower 90 percent confidence limit of the experimentally determined dose-response slope from the carcinogenicity studies for extrapolation to a maximum exposure level with appropriate adjustments to account for drug usage and human consumption patterns and for the differences between daily food intake per unit of body weight of the laboratory animal and of man. (i) If the data indicate that some linearizing transformation other than the probit-log transformation used in the modified Mantel-Bryan procedure better describes the observed response and has a biological rationale, then this other linearizing transformation will be used for the extrapolation. (ii) In the event that both significant noncarcinogenic harmful effects and carcinogenic effects are observed during testing, the lowest level for the regulatory assay sensitivity as determined for the different effects shall be adopted.

(7) The sensitivity of the regulatory assay method as defined above, the method, and a definition of the criteria used to establish a reliable positive finding shall be published in the FEDERAL REGISTER.

(8) The withdrawal period for the compound shall be based, using the regulatory assay method and/or other suitable methods, on the time required after the last dosage for tissue levels of the parent compound and/or its metabolites and/or any affected endogenous compounds to fall below the required regulatory assay sensitivity.

(9) The withdrawal period shall be the longer of either (i) the number of days required for tissue levels to be depleted to less than the maximum exposure level plus a safety factor to account for animal to animal variation as determined by appropriate confidence interval techniques or (ii) the number of days required for any affected endogenous compound to return to a normal level plus a safety factor to account for animal to animal variation. Current livestock management techniques may justify a longer withdrawal period. The normal level of any affected endogenous compound shall be established as described in paragraph (c) of this section.

(10) Based on tissue depletion studies and animal management practices, conditions of use that are reasonably certain to be followed in practice shall be specified for the compounds so that, if followed, they assure that no residue shall occur in food produced from treated animals.

(11) Notwithstanding a determination pursuant to this paragraph of the required level of sensitivity of the regulatory assay method, if a regulatory assay method of lower sensitivity is later developed and validated the Commissioner will adopt that more sensitive method and publish it in the FEDERAL REGISTER even though its development was not required.

(c) Endogenous compounds, defined as those compounds which are present in and are produced by the normal animal and are not required from an external source, are subject to the following requirements:

[1] Copies may be obtained from: Director, Division of Nutritional Sciences (VM–100), Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

(1) Metabolism studies shall be conducted in the target species to identify and quantify the metabolites of the parent compound and the concentrations of the compound and its metabolites in specific tissues ("tissues" include milk and eggs, if applicable). The effect of the endogenous compound on tissue levels of related endogenous compounds also shall be determined.

(2) Degradation of the compound and/or its metabolites during the period of time after slaughter that the edible tissue would normally be held under storage conditions and the impact of cooking on the compounds and/or its metabolites in question shall be determined.

(3) Animals containing tissue levels of endogenous compounds above the normal due to the administration of endogenous compounds may not be marketed for human consumption. Thus, neither tests for carcinogenicity nor standard toxicity testing shall be required for endogenous compounds.

(4) The naturally occurring or background tissue levels of endogenous compounds and/or their metabolites and/or other related endogenous compounds in the target species shall be determined in studies designed to show the effect of geographical location, stage of estrus, age, etc., on normal animals receiving no external source of the endogenous compound. The tissue distribution will be used to establish the required sensitivity of the regulatory assay method. The required sensitivity of the regulatory assay method will be that value of the distribution which is exceeded by only one percent of the normal animals.

(5) The sensitivity of the regulatory assay method as defined above, the method, and a definition of the criteria used to establish a reliable positive finding shall be published in the FEDERAL REGISTER.

(6) The withdrawal period for the compound shall be based using the regulatory assay method and/or other suitable methods, on the time required after the last dosage for the tissue levels of the parent compound and/or its metabolites and or any affected other related endogenous compounds to return to the median background level of contemporary controls. The withdrawal period shall be the number of days required for tissue levels of any affected endogenous compounds to return to the median background level plus a safety factor to account for animal to animal variation as determined by appropriate confidence interval techniques. Current livestock management techniques may justify a longer withdrawal period.

(7) The characteristics of the distribution of tissue levels of the compound normally found in animals not exposed to external sources of the compound and the specified conditions of use shall be published in the FEDERAL REGISTER as part of the approval of any endogenous drug compound.

(8) Based on tissue depletion studies and animal management practices, a withdrawal period and conditions of use that are reasonably certain to be followed in practice shall be specified for the compound so that, if followed, they assure that no residue shall occur in excess of the established normal level in food from untreated animals.

(d) Prior to approval, the adequacy of the regulatory assay method shall be determined by validation of the method in appropriate Food and Drug Administration laboratories and other laboratories. The validation shall determine the feasibility, specificity, accuracy, and precision of the method. This validation of an assay method used for regulatory purposes shall be based on the following criteria:

(1) The method shall be capable of reproducibly extracting, at the required level of sensitivity, the significant compounds from target tissues obtained from treated animals, as well as from tissues containing known added amounts of the compounds.

(2) The method shall be capable of measuring residues with a sufficient degree of specificity, precision, and accuracy to preclude the occurrence of false negatives or false positives.

(3) The equipment, reagents and compounds used in the assay shall be commercially available. Any required specialization in terms of equipment or personnel shall be consistent with that normally available in a modern well-equipped analytical control laboratory.

(4) The time required for completion of the assay shall not be so excessive as to delay regulatory action.

(5) The assay shall offer minimal hazard in the laboratory.

(e) After publication in the FEDERAL REGISTER of an assay method in accordance with paragraphs (b) through (d) of this section, compliance shall be determined as follows:

(1) Samples of the food produced from appropriate animals will be routinely collected and evaluated using the regulatory assay method(s).

(2) Any sample subject to paragraph (b) of this section yielding a residue of the compound at or above the published level of sensitivity of the method will be liable to regulatory action.

(3) Any sample subject to paragraph (c) of this section yielding a residue of the compound at or above the published level of sensitivity of the method will be subject to investigation. Any such residue which is determined to be the result of improper use of the compound will be liable to regulatory action.

(4) No regulatory action may be based on the measurement of a value which is below the established level of sensitivity of the approved regulatory assay method(s) as published in the FEDERAL REGISTER.

(f) The provisions of this section shall be applicable to all new animal drug applications, including supplements, approved by the Food and Drug Administration subsequent to the effective date of the final regulation, except that supplemental applications meeting the requirements of § 135.13a(d) or that in the opinion of the Commissioner otherwise protect the public health will be permitted to be put into effect in accordance with § 135.13a(e) through (k).

(g) The provisions of this section shall be applicable to existing approvals of new animal drugs in accordance with the following priorities:

(1) The Commissioner will review existing zero tolerances (no residues) to determine whether the drugs involved should be the subject of finite or negligible residues. Those drugs for which finite or negligible residues are established are not subject to the provisions of paragraphs (b) or (c) of this section.

(2) Those drugs for which the Commissioner has determined the appropriateness of a zero tolerance (no residue) will be the subject of a notice published in the FEDERAL REGISTER or a letter to every holder of a new animal drug application establishing a time within which the provisions of this section shall be satisfied. Notices already published in the FEDERAL REGISTER and letters already sent by the Food and Drug Administration requiring additional studies and/or a more sensitive regulatory assay method for a drug subject to a zero tolerance shall remain in effect, and the provisions of this section shall be used in determining compliance with the requirements of the act pursuant to those notices and letters. The Commissioner will immediately proceed to withdraw approval of any drug on the basis of data or information indicating a health hazard or a failure to undertake studies necessary to comply with the provisions of this section.

Interested persons may, on or before September 17, 1973, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be viewed in the above office during working hours, Monday through Friday.

Dated: July 13, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-14746 Filed 7-18-73;8:45 am]

Social Security Administration

[20 CFR Part 405]

[Reg. No. 5]

FEDERAL HEALTH INSURANCE FOR THE AGED AND DISABLED

Payment for Services of Physicians in Teaching Hospitals, for Physician Costs to Hospitals and Medical Schools, and for Volunteer Services

Notice is hereby given, pursuant to the Administrative Procedure Act (5 U.S.C. 552 et seq.) that the amended regulations set forth in tentative form below are proposed by the Acting Commissioner of Social Security, with the approval of

01137

Materials Importation Act of 1966 (Public Law 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (37 F.R. 3892 et seq.).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C.

Docket No. 72-00287-98-29800. Applicant: University of Hawaii, High Energy Physics Group, 2565 The Mall, Physical Science Building, Honolulu, Hawaii 96822. Article: Automatic Film Measuring Device. Manufacturer: Laser-Scan, Ltd., United Kingdom. Intended use of article: The article is intended to be used in bubble-chamber research in studies of three dimensional events as recorded on film occurring in high energy physics.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States. Reasons: The foreign article is specially designed to examine photographic records of events occurring in a bubble chamber. We are advised by the National Bureau of Standards (NBS) in its memorandum dated June 7, 1972, that the general specifications of the article are pertinent to the purposes for which the article is intended to be used. NBS also advises that it knows of no domestically manufactured instrument which is scientifically equivalent to the foreign article for the applicant's intended use.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

SETH M. BODNER,
Director,
Office of Import Programs.

[FR Doc.72-12187 Filed 8-3-72;8:49 am]

UNIVERSITY OF WASHINGTON

Notice of Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to section 6(c) of the educational, Scientific, and Cultural Materials Importation Act of 1966 (Public Law 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (37 F.R. 3892 et seq.).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C.

Docket No. 72-00090-55-17500. Applicant: University of Washington, Department of Oceanology, Seattle, Wash. 98195. Article: Recording current meter, Model 4. Manufacturer: Ivar Aanderaa, Norway. Intended use of article: The article is intended to be used to monitor current speed and direction, and water temperature during deployment of the current meter in the 2,600-meter-deep Greenland-Spitsbergen passage. Comments: No comments have been received with respect to this application.

Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States. Reasons: The foreign article provides self-contained operation and recording for a duration of 1 year. The most closely comparable domestic instrument, the Model 502, manufactured by Hydro Products, San Diego, Calif., provides the capabilities described above for 30 days. We are advised by the National Bureau of Standards (NBS) in its memorandum dated June 23, 1972, that the longer duration of self-contained operation of the foreign article is pertinent to the purposes for which the article is intended to be used. For this reason we find that the Model 502 is not of equivalent scientific value to the foreign article for such purposes as the article is intended to be used.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

SETH M. BODNER,
Director,
Office of Import Programs.

[FR Doc.72-12188 Filed 8-3-72;8:49 am]

YALE UNIVERSITY

Notice of Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Public Law 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (37 F.R. 3892 et seq.).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C.

Docket No. 72-00382-33-43400. Applicant: Yale University, Purchasing Department, 260 Whitney Avenue, New Haven, CT 06520. Article: Micromanipulator. Manufacturer: A.B. Transvertex, Sweden. Intended use of article: The article will be used in research to obtain intracellular recordings from mitral cells and other cells in the olfactory bulb. Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States.

Reasons: The foreign article provides precise penetration of cell membranes through electrode advance in a stepping manner. We are advised by the Department of Health, Education, and Welfare (HEW) in its memorandum dated July 7, 1972, that the capability described above is pertinent to the purposes for which the article is intended to be used. HEW also advises that it knows of no comparable domestic apparatus which is scientifically equivalent to the foreign article for such purposes as the article is intended to be used.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

SETH M. BODNER,
Director,
Office of Import Programs.

[FR Doc.72-12189 Filed 8-3-72;8:49 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Dockets Nos. FDC-D-452, 494; NADA's Nos. 11-295V, 9525, etc.]

DIETHYLSTILBESTROL

Order Denying Hearing and Withdrawing Approval of New Animal Drug Applications for Liquid and Dry Premixes, and Deferring Ruling on Implants

In the FEDERAL REGISTER of March 11, 1972 (37 F.R. 5264), a notice of opportunity for a hearing was published announcing that the Commissioner of Food and Drugs proposed to issue an order under section 512(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of new animal drug applications for diethylstilbestrol (DES) liquid premixes for use in the manufacture of feeds for cattle and sheep.

In the FEDERAL REGISTER of June 21, 1972 (37 F.R. 12251), a notice of opportunity for a hearing was published announcing that the Commissioner proposed to issue an order under section 512(e) of the act withdrawing approval of new animal drug applications for DES liquid and dry premixes for use in the manufacture of feeds for cattle and sheep and for DES implants for cattle and sheep. This notice stated that the earlier notice of opportunity for a hearing with respect to DES liquid premixes would be acted upon at the same time.

Objections and requests for a public hearing were received from 15 of the 25 holders of the new animal drug applications for DES liquid and dry premixes for use in the manufacture of animal feed for cattle and sheep. For the reasons stated below, a hearing is denied with respect to these new animal drug applications. The new animal drug applications for such products are hereby withdrawn, effective immediately.

This matter is a regulatory, not a public health, problem. The animal feeding industry, the pharmaceutical industry, and the U.S. Department of Agriculture have been unable to come forward with restrictions and controls on the use of DES in animal feed that are reasonably certain to be followed in practice and that will result in the absence of detectable residues in the edible portions of the animals. Accordingly, the law requires that use of the drug must be discontinued.

Because there is no evidence of a public health hazard, however, there is no justification for an abrupt disruption of the production of the Nation's meat supply. An immediate ban on use of DES in feed could result in an unwarranted public concern and an unjustified increase in meat prices. It is estimated that there is about a 4-months supply of DES liquid and dry premixes already manufactured and at various stages in the chain of distribution. Accordingly, the Commissioner has determined that the manufacture of liquid and dry premixes will be discontinued effective immediately. Feeding of DES will be discontinued as soon as existing supplies are used up, but no later than January 1, 1973. This will permit both an orderly phaseout of the use of the drug in animal feed and an opportunity for the animal feeding industry to switch to DES implants, to other implants, or to other methods of meat production. DES implants and other implants have been shown to be approximately as effective for growth promotant purposes as DES in feed.

Objections and requests for a public hearing were also received with respect to all new animal drug applications for DES implants. For the reasons stated below, the Commissioner has concluded that the further testing now underway and scheduled to be completed within several weeks should be concluded before a ruling is made on these objections and requests for a hearing. Accordingly, such a ruling is deferred pending completion of those tests, at which time it will promptly be made and published in the FEDERAL REGISTER.

DES LIQUID AND DRY FEED PREMIXES

The following new animal drug applications for liquid and dry feed premixes for cattle and sheep were covered by the March 11 and June 21 notices of opportunity for a hearing:

Elanco Products Co., Post Office Box 750, Indianapolis, Ind. 46206. NADA's Nos. 9525, 11090, and 42162.

Pfizer, Inc., New York, N.Y. 10017. NADA's Nos. 9767 and 9770.

Walnut Grove Products, Division of W. R. Grace Co., Atlantic, Iowa 50022. NADA No. 10132.

Dawes Laboratories, Chicago, Ill. 60632. NADA's Nos. 10421, 11485, and 34916.

Simonsen Manufacturing Co., Quimby, Iowa 51049. NADA No. 10566.

Hess and Clark, Division of Rhodia, Inc., Ashland, Ohio 44805. NADA's Nos. 11205, 44344, 45982, and 45981.

Peter Hand Foundation, Inc., Waukegan, Ill. 60085. NADA No. 14773.

Thompson-Hayward Chemical Co., Kansas City, Kans. 66106. NADA's Nos. 35019 and 35017.

Feed Additives, Inc., Fremont, Nebr. 68025. NADA's Nos. 36313 and 37869.

Dale Alley Co., Post Office Box 444, St. Joseph, Mo. 64501. NADA's Nos. 36671 and 36554.

Standard Chemical Manufacturing Co., Omaha, Nebr. 68103. NADA's Nos. 36976 and 34735.

National Oats Co., East St. Louis, Ill. 62205. NADA's Nos. 37148 and 37541.

Texas Nutrition & Service Co., Fort Worth, Tex. 76106. NADA's Nos. 38507, 38510, and 39509.

Bresley-Koelling, Inc., Ord, Nebr. 68862. NADA No. 39491.

Feed Products, Inc., Denver, Colo. 80211. NADA's Nos. 39716, 39718, 39717, and 39715.

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N.J. 07065. NADA's Nos. 39772, 42840, and 10261.

Chemetron Corp., Chicago, Ill. 60611. NADA No. 42355.

Farmland Industries, Kansas City, Mo. 64116. NADA No. 42702.

Western Farmers Association, Seattle, Wash. 98111. NADA No. 44526.

Western Feed Supplements, Ellensburg, Wash. 98926. NADA No. 40014.

Ultra Life Laboratories, Inc., East St. Louis, Ill. 62201. NADA No. 38682.

Square Deal Fortification Co., Kouts, Ind. 46347. NADA No. 39161.

Falstaff Brewing Corp., St. Louis, Mo. 63166. NADA No. 44795.

American Cyanamid Co., Princeton, N.J. 08540. NADA No. 10258.

S. B. Penick Co., New York, N.Y. 10008. NADA No. 36479.

Of these all but the following firms submitted objections and requests for a hearing:

Peter Hand Foundation, Inc., Waukegan, Ill. 60085.

Feed Additives, Inc., Fremont, Nebr. 68025.

Dale Alley Co., St. Joseph, Mo. 64501.

National Oats Co., East St. Louis, Ill. 62205.

Texas Nutrition & Service Co., Fort Worth, Tex. 76108.

Feed Products, Inc., Denver, Colo. 80211.

Ultra Life Laboratories, Inc., East St. Louis, Ill. 62201.

Square Deal Fortification Co., Kouts, Ind. 46347.

Falstaff Brewing Corp., St. Louis, Mo. 63166.

American Cyanamid Co., Princeton, N.J. 08540.

The Commissioner has concluded that these objections, in the light of new evidence from radioactive tracer studies on animals withdrawn from DES feed for 7 days, fail to show reasonable grounds for a hearing on a basis of evidence.

Virtually all of the objections and requests for a hearing fail to comply with 21 CFR 135.15(b), which requires that the objector file a full factual analysis of the data upon which it relies. In this case, the objections received generally rest upon mere allegations or denials and fail to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing.

The objections contend that there are genuine and substantial issues of fact requiring a hearing as follows:

1. The number of violative residues may not actually have increased and, in fact, may have decreased.

2. New and more sophisticated laboratory methodology may be detecting residues at a level that previously was not detected.

3. The validity of the new methodology for detection has not adequately been established at the lower levels.

4. Some of the positives reported may be false positives rather than DES residues.

5. The compound found in animal livers is the monoglucuronide ester, not DES, and this ester has not been tested for carcinogenicity.

6. The level of compliance necessary to satisfy the statutory standard of "reasonably certain to be followed in practice" is unclear and, in any event, a degree of violation was contemplated by Congress.

7. The directions for use of DES may presently be inadequate and may be capable of improvement to assure the safe use of DES.

8. Present manufacturing controls may be inadequate to prevent cross-contamination of withdrawal feeds, and may be capable of improvement to preclude such cross-contamination.

9. A substantial portion of the current violative residues may be the result of cross-contamination of withdrawal feeds rather than of misuse of the drug.

10. Some violative residues may be the result of other sources of DES contamination, rather than misuse of the drug, and more restrictive controls over DES and of animals on withdrawal feed may reduce or eliminate such violative residues.

11. There may be alternative restrictive conditions under which DES may safely be used, such as disposal of animal livers, restrictions on the size or capability of feed lots authorized to use the drug, or other means of testing cattle for DES withdrawal prior to slaughter.

12. Withdrawal of approval of DES may have adverse effects on the environment as a result of increased manure production per day and increased number of days required for feeding to a specific weight.

These objections were stated largely as questions, without a presentation or analysis of the data necessary to support hypotheses advanced and without specific data from tests designed to answer the questions or to support specific proposals or recommendations sufficient to correct the problems demonstrated. Changes in labeling and new restrictions to reduce or eliminate cross-contamination, misuse of the drug, or other sources of violative residues are properly requested through supplemental new animal drug applications rather than through a hearing.

The effectiveness of DES as a growth promotant has not been and is not questioned. Until Friday, July 28, 1972, the Commissioner was unaware of the existence of any data indicating that use under the conditions contained in the approved label would result in detectable residues of DES in the edible portion of animals. Prior studies, using the most sensitive research tools available, showed no detectable residues in the animal liver after 48 hours and even in inedible waste after 132 hours. On December 8, 1971 (36 F.R. 23292), the withdrawal period

01139

was extended from 48 hours to 7 days as a prudent precautionary measure to provide an extra margin of safety.

On Friday, July 28, 1972, the Commissioner was informed of the results of a research study undertaken by the U.S. Department of Agriculture in which it was found, using radioactive-tagged DES in six steers, that detectable residues occurred in the liver from a single 10 mg. oral dose of DES after withdrawal for 3, 5, and even 7 days. Two steers each were slaughtered at 72, 120, and 168 hours after being fed the radioactive-tagged DES. The results of that study are as follows:

Hours after withdrawal	Parts per billion	Residue in animal liver
72	1.06	0.41
120	.65	.15
168	.21	.52

These cattle were fed 10 mg. DES twice daily for a sufficient time period to establish the usual feeding pattern and were then fed a single radioactive-tagged 10 mg. dose of DES. Because only this split dose was tagged, FDA and USDA scientists project from these data that, even after withdrawal for 7 days, some cattle fed the approved level of 10 mg. DES twice daily in liquid or dry feed could be expected to have up to 1 p.p.b. DES in the liver.

From earlier data, it was thought that the half-life of DES in the animal was 12 hours. The new data show that, after 3 days, the elimination rate appears to decrease substantially. Because the experiment has not been carried out for longer than 7 days, it is impossible at this time to determine the rate of residue elimination beyond this period. It is hypothesized that, after 30 days withdrawal, the residue would be reduced to the practical equivalent of zero. There are, however, no data available to substantiate this hypothesis. The law requires that the holder of a new animal drug application submit all data necessary to show that it is possible to use the drug without any residue remaining in the edible portions of the animal. In the absence of such data, the new animal drug application must be withdrawn.

Even if data were available to demonstrate a suitable withdrawal period, it is now questionable whether a sufficiently precise regulatory surveillance method is available to permit continued approval of the drug in animal feed. In view of the new USDA study, it now appears that the test results thought possibly to be false positives may indeed have been true positives. The Commissioner is unaware of any data which could reasonably be interpreted to show that a 30-day feed withdrawal period, which in any event can only be hypothesized as a suitable withdrawal period, would be reasonably certain to be followed in practice. Even if a 30-day withdrawal period were ordered, no regulatory surveillance method now available would be sufficiently sensitive to detect violations of this requirement. The imposition of new and more stringent restrictions on the use of DES in feed, such as an increased withdrawal period, measures to avoid cross-contamination, and similar requirements, is therefore no longer a controlling factor in view of the new USDA study showing that even proper use of the drug under existing restrictions may result in violative residues.

Neither the new USDA study no other information available to the Commissioner demonstrates that there are residues of DES in muscle tissue, which represents the major source of meat for the country. This raises the possibility of permitting continued use of DES in animal feed but of destroying beef livers and kidneys from any animal so fed. The Commissioner has concluded, however, that there are insufficient scientific data on which to base a clear decision when DES residues will not be found in muscle tissue. In addition, no evidence has been submitted with the objections or is otherwise known to the Commissioner that would permit a conclusion that a requirement that the liver and kidneys of cattle fed DES must be destroyed would be reasonably certain to be followed in practice. The maintaining of identification and records to differentiate between animals fed DES and animals not fed DES would be extremely difficult. Such a control system would require a significant change in the method of handling cattle in this country, the complexity of which does not permit such institution hurriedly or on the basis of conjecture. If any such system is to be developed, it must be the subject of pilot programs conducted through investigational new animal drug plans that will demonstrate its feasibility and after further radioactive tracer studies which show the exact time when residues in muscle tissue are eliminated.

The new USDA study involved only cattle, and not sheep. The information available to the Commissioner, however, shows that the problem of DES residues is approximately the same in both animals. Previous data establish roughly the same level of residue under the same conditions of DES use in feed. Violative residues have been found in sheep at roughly the same rate as in cattle. The two animals are biologically quite similar. Accordingly, the Commissioner concludes that there is no basis for distinguishing between them with respect to approval of DES for use in feed.

Finally, the Commissioner has reviewed the potential environmental impact of this action. It has been estimated that there would be a substantial increase in animal waste and in available nitrogen if DES were to be withdrawn from use as an animal growth promotant. In view of the fact that this action permits the continued use of DES implants pending the results of a study now in progress, as described below, and in view of the availability of at least one alternative implant drug, the Commissioner is unable to conclude that the environmental aspects of this problem outweigh the clear requirements of the law. Pursuant to proposed § 6.3(c) of the proposed regulations governing environmental impact considerations published in the FEDERAL REGISTER of July 12, 1972 (37 F.R. 13636), the Commissioner has concluded that the Federal Food, Drug, and Cosmetic Act requires immediate action on this matter without preparation and filing of a draft or final environmental impact statement. By publication of this order, the Council on Environmental Quality and the public are so informed.

For the foregoing reasons, therefore, the Commissioner concludes that the objections fail to demonstrate the existence of a genuine and substantial issue of fact and, accordingly, a hearing is denied with respect to the use of DES in liquid and dry premixes for feed for cattle and sheep.

This action is required under the strict terms of sections 512(d)(1)(H) and 512(e)(1)(B) of the act. These provisions, which contain the so-called Delaney Clause, require that there be no detectable residue. The new USDA study clearly shows residues at levels that are in the range of current detection methodology; new detection methodology is being developed that would be significantly more sensitive. Thus, under the law there is no alternative but to withdraw approval of the drug, even though there is no known public health hazard resulting from its use.

It should be emphasized that the Commissioner has no reason to believe that use of DES in animal feed represents a public health hazard. No human harm has been demonstrated in over 17 years of use. Under the law, however, this continued use of the drug may no longer be permitted.

The Commissioner has concluded that withdrawal of approval of the new animal drug applications for the DES liquid and dry premixes should be effective immediately. This means that these premixes may not be manufactured effective as of the date of publication of this order in the FEDERAL REGISTER.

In the Commissioner's judgment, although withdrawal of approval is warranted by the facts, the continued use of meat from animals fed DES, of feed already containing DES, and of premixes already manufactured does not present a health hazard. Approval is being withdrawn not because there is a proof of danger from DES, but because at this time the new USDA study shows a lack of clear and convincing proof that the requirements of the law are fully satisfied. Accordingly, no recall or cessation of shipment or use of existing stocks is warranted. As long as there is no further manufacturing of these premixes, existing supplies of feed and premixes may be used in an orderly phaseout of the drug. In order to place an end point on this phase out, the Commissioner has determined that all feeding of DES shall be discontinued by January 1, 1973.

01140

DES IMPLANTS

The following new animal drug applications for DES implants for cattle and sheep were covered by the June 21 notice of opportunity for a hearing:

Pfizer, Inc., New York, N.Y. 10017. NADA's Nos. 9783 and 11356.
Vineland Laboratories, Inc., Subsidiary of Damon, Vineland, N.J. 08360. NADA No. 10964.
Hess & Clark, Division of Rhodia, Inc., Ashland, Ohio 44805. NADA No. 12553.
O. M. Franklin Serum Co., Denver, Colo. 80216. NADA No. 15274.
Fort Dodge Laboratories, Fort Dodge, Iowa. 50501. NADA No. 31446.
E. R. Squibb & Sons, New Brunswick, N.J. 08902. NADA No. 11365.

The new USDA study did not include implants. Earlier testing has shown that implants result in no detectable residues, and that there is at least a 10-fold, and probably a 30-fold or greater, difference in the potential for such residues. Thus far, the USDA in its sampling program has not found a single residue resulting from implants alone, but the significance of that fact is uncertain because there is no information on the amount of cattle administered DES solely by implant and the USDA sampling has uncovered instances in which a residue was found in animals fed DES and implanted at the same time.

Use of implants represents a substantially reduced total dose of DES as compared with use of medicated feed. The 20 mg. per day normal dose of DES in feed represents 3,000 mg. per head over the customary 150 days of feeding. During the same period, the maximum dose of DES that would be expected from the use of implants would be approximately 100 mg. per head, based upon the approved use of three 12 mg. implants for a 60-day period, and this dose would ordinarily be less because a smaller implant is customarily used when the animal is younger. This difference represents at least a 30-fold dosage factor, with respect to both the possibility of residues and any potential environmental implant.

USDA has previously begun preparations for a radioactive tracer study using implants. The test using these radioactive-tagged implants has just begun, and the results will be available within several weeks.

The Commissioner has therefore concluded that it is premature to rule at this time on the objections and requests for a hearing with respect to DES implants. A ruling on this matter will await the results of the USDA implant study now underway.

At the present time, the Commissioner has no reason to believe that DES implants raise a public health hazard. Thus, while it is prudent to pursue and to resolve existing scientific questions about DES implants, it is unnecessary to remove existing implants or to be concerned about the safety of meat from animals implanted with DES.

CONCLUSION

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (Sec. 512, 82 Stat. 343-51; 21 U.S.C. 360b) and under authority delegated to the Commissioner (21 CFR 2.120), the requests for evidentiary hearings with respect to the above-listed new animal drug applications for DES liquid and dry premixes for cattle and sheep are denied and approval of the applications, including all amendments and supplements thereto, is hereby withdrawn. Manufacturing of such premixes shall stop immediately, and feeding of existing supplies of such premixes shall stop as soon as existing supplies are exhausted but in any event no later than January 1, 1973. The Commissioner defers a ruling on withdrawal of the above listed new animal drug applications for DES implants for cattle and sheep. This order shall be effective on its date of publication in the FEDERAL REGISTER (8-4-72).

Dated: July 31, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.72-12286 Filed 8-3-72;8:55 am]

ATOMIC ENERGY COMMISSION

[Dockets Nos. 50-369, 50-370]

DUKE POWER CO.

Notice Rescheduling Hearing

In the matter of Duke Power Co. (William B. McGuire Nuclear Station, Units 1 and 2), Dockets Nos. 50-369 and 50-370.

Notice is hereby given that the hearing in the captioned proceeding previously set to reconvene on August 8, 1972, has been rescheduled to 10 a.m. on Wednesday, September 6, 1972, at the:

Mecklenberg County Administration Building, Commissioner's Meeting Room, Fourth Floor, 720 East Fourth Street, Charlotte, NC 28202.

Issued: July 31, 1972, Washington, D.C.

ATOMIC SAFETY AND LICENSING BOARD,

ROBERT M. LAZO,
Chairman.

[FR Doc.72-12212 Filed 8-3-72;8:50 am]

[Docket No. 50-410]

NIAGARA MOHAWK POWER CORP.

Notice of Receipt of Application for Construction Permit and Facility License and Applicant's Environmental Report; Time for Submission of Views on Antitrust Matter

Niagara Mohawk Power Corp., 300 Erie Boulevard West, Syracuse, NY 13202, pursuant to section 103 of the Atomic Energy Act of 1954, as amended, has filed an application dated June 7, 1972, for authorization to construct and operate a single cycle, forced circulation, boiling water nuclear reactor at its site, located in the town of Scriba, Oswego County, N.Y. The site consists of 900 acres and is located 300 feet due west of Nine Mile Point Unit 1 (Docket No. 50-220) on the southeast shore of Lake Ontario, approximately 7 miles northeast of the city of Oswego.

The proposed nuclear facility, designated by the applicant as Nine Mile Point Unit 2, is designed for initial operation at approximately 3,300 megawatts (thermal) with a net electrical output of approximately 1,100 megawatts.

Any person who wishes to have his views on the antitrust aspects of the application presented to the Attorney General for consideration shall submit such views to the Commission within sixty (60) days after July 14, 1972.

A copy of the application is available for public inspection at the Commission's Public Document Room, 1717 H Street NW., Washington, DC 20545, and at the Oswego City Library, 120 East Second Street, Oswego, NY 13126.

Niagara Mohawk Power Corp. has also filed, pursuant to the National Environmental Act of 1969 and the regulations of the Commission in Appendix D to 10 CFR Part 50, a report entitled "Applicant's Environmental Report—Construction Permit Stage," dated June 1972. The report has been made available for public inspection at the aforementioned locations. The report, which discusses environmental considerations related to the proposed construction of Nine Mile Point Unit 2, is also being made available at the New York State Office of Planning Services, 488 Broadway, Albany, NY 12207, and at the Central New York Regional Planning and Development Board, 321 East Water Street, Syracuse, NY 13202.

After the report has been analyzed by the Commission's Director of Regulation or his designee, a draft environmental statement related to the proposed action will be prepared by the Commission. Upon preparation of the draft environmental statement, the Commission will, among other things, cause to be published in the FEDERAL REGISTER a summary notice of availability of the draft statement. The summary notice will request comments from Federal agencies, State and local officials, and interested persons on the proposed action and on the draft statement. The summary notice will also contain a statement to the effect that comments will be made available when received.

Dated at Bethesda, Md., this 6th day of July 1972.

For the Atomic Energy Commission.

ROGER S. BOYD,
Assistant Director for Boiling Water Reactors, Directorate of Licensing.

[FR Doc.72-10706 Filed 7-13-72;8:45 am]

[Docket No. 50-135]

WALTER REED ARMY MEDICAL CENTER

License Termination Order

The Atomic Energy Commission (the Commission) has found that the Walter

01141

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 27]

QUALITY STANDARD FOR CANNED CHERRIES

Proposed Revision of Blemish Limitation

Notice is given that a petition has been filed by the National Canners Association, 1133 20th St., NW., Washington, DC 20036, proposing that the standard of quality for canned cherries (21 CFR 27.31) be amended by:

(1) Changing the definition of a blemished cherry; and

(2) Increasing the aggregate area of the blemish from $\frac{3}{16}$ inch to $\frac{9}{32}$ inch in diameter.

Grounds set forth in the petition in support of the proposal are that: (1) The proposed change in the definition of a blemished unit would be consistent with objections received to an order, published in the FEDERAL REGISTER on February 23, 1971 (36 FR 3364) ruling on a proposed cherry pie standard of quality (21 CFR 28.2). These objections requested that the $\frac{3}{16}$ inch diameter limit for blemished units be changed to a $\frac{9}{32}$ inch diameter limit. The Commissioner of Food and Drugs granted this request in the FEDERAL REGISTER of June 13, 1973 (38 FR 15503).

(2) Mechanical harvesting and bulk handling in tanks of water have replaced the traditional hand picking and handling. As a result there has been a greatly increased problem with a mild form of discoloration known as "tank or water scald" which results in minor color variation but does not affect the tissues or eating quality or the cherries.

(3) Since the present standard was established 32 years ago, changes in cultural practices have resulted in the production of larger and softer cherries. Presently, there are as few as 100 to 110 cherries per pound as compared to 140 to 150 per pound when the standard was adopted. The larger, softer cherries have aggravated the blemish problem because they are more susceptible to blemishes and contain a greater surface area compared to the permitted area of skin discoloration.

(4) Increasing the area of the blemish to 9/32 inch would bring the quality standard for canned cherries (21 CFR 27.31) into agreement with the present voluntary U.S. Department of Agriculture standard for grades of frozen cherries.

(5) The proposed change will insure consumers a continued supply of canned cherries without significantly affecting the quality.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 701, 52 Stat. 1046, 1055 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 341, 371) and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Part 27 be amended in § 27.31 by revising paragraph (a)(5) to read as follows:

§ 27.31 Canned cherries; quality; label statement of substandard quality.

(a) * * *

(5) Not more than 15 percent by count of the cherries in the container are blemished with scab, hail injury, discoloration, scar tissue or other abnormality. A cherry showing skin discoloration (other than scald) having an aggregate area exceeding that of a circle 9/32 inch in diameter is considered to be blemished. A cherry showing discoloration of any area but extending into the fruit tissue is also considered to be blemished.

* * * * *

Interested persons may, on or before September 17, 1973 file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: June 20, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-14749 Filed 7-18-73;8:45 am]

[21 CFR Part 135]

COMPOUNDS USED IN FOOD-PRODUCING ANIMALS

Procedures for Determining Acceptability of Assay Methods Used for Assuring the Absence of Residues in Edible Products of Such Animals

The Federal Food, Drug, and Cosmetic Act requires that compounds administered to animals as food additives, color additives, or animal drugs be shown to be safe for use. The term "safe" refers to the health of man or animal under section 201(u) of the act. In evaluating the safety of such compounds used in food-producing animals, consideration must be given to the safety of possible residues in the products of those animals which are a source of food for man. When there is insufficient evidence to establish that a finite or negligible residue of the compound is safe in human food, or when the anticancer clauses contained in sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B) of the act are applicable, a zero tolerance (no residue) must be required. (Under the provisions of the anticancer clauses no compound may be administered to animals which are raised for food production if such compound has been shown to induce cancer when ingested by man or animal, unless such compound will not adversely affect the animal and no residues, as determined by methods of analysis prescribed or approved by the Secretary, are found in the edible products of such animals under conditions of use specified in labeling and reasonably certain to be followed in practice. A decision is then required as to whether a practicable method exists to determine the absence of such residues in food, under sections 409(b)(2)(D), 512(b)(7), and 706(b)(5)(A)(iv) of the act.

The Commissioner of Food and Drugs has determined that it would be in the public interest to set forth the principles involved in application of these safety provisions of the law with respect to the adequacy of the sensitivity of the required regulatory assay method for monitoring compounds which may be administered to food-producing animals, but for which no residue is permitted in human food. Therefore, a new regulation is proposed to establish the minimum standards for determining the acceptability of assay methods used to assure the absence of residues in edible products of such animals. These proposed regulations do not apply to drugs for which a finite or negligible residue is established as safe for human food.

The proposed new regulation will apply to two classes of compounds administered to food-producing animals: (1) Exogenous compounds, defined as those compounds which are not produced by the normal animal and are not required for normal animal body function (e.g., diethylstilbestrol), and (2) Endogenous compounds, defined as those compounds which are present in and produced by the normal animal and are not required from an exogenous source (e.g., estradiol).

In evaluation of the safety of compounds of both classes the initial testing must involve detailed metabolism studies in the target species. Radiotracer studies are usually the method of choice. The purpose of these studies will be to identify the metabolites of the compound, both qualitatively and quantitatively, and the concentrations of the compound and its metabolites in specific tissues ("tissues" include milk and eggs, if applicable). Another aspect of these studies will be the determination of the effect of the administration of the compound on tissue levels of related endogenous compounds.

For acceptable studies, it is necessary to follow the degradation of the compound and/or its metabolites after slaughter and during the period that the edible tissue would normally be held under storage conditions as well as to determine the impact of cooking at appropriate temperatures on the compounds in question.

EXOGENOUS COMPOUNDS

Determination as to whether an exogenous compound and/or its metabolites will require carcinogenicity testing will be based on the results of the metabolism studies, standard toxicity testing, structural relationships of the compound and or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended use pattern of the compound. Tests for carcinogenicity will be routinely required for any new compound for which a priori knowledge is incomplete and which is intended to be used for disease prophylaxis and, or production purposes (e.g., increased rate of weight gain, estrus synchronization, etc.).

01142

If it is determined that tests for carcinogenicity are not required, or if the results of such tests are negative, consideration leading to approval will be based on standard toxicological procedures. These procedures will include, in addition to subacute studies in a minimum of two species, such studies as multi-generation reproduction studies, teratological and any other special studies which may be indicated from the nature of the biological action of the compound, including life-time studies. These studies will involve collecting data from appropriately designed dose-response experiments that demonstrate a maximum "no harmful effect level" as well as a minimum "harmful effect level" in appropriate animal species.

Where a residue is permitted as safe in human food (either as a finite tolerance level or as a negligible residue of less than a specified level), the sensitivity of the assay method will be required to meet the specified level, and the other provisions of this proposed new regulation relating to the required sensitivity of the method will be inapplicable. Where no residue (zero tolerance) is permitted, the provisions of this proposed new regulation are fully applicable.

Under the proposed new regulation the dose-response slope estimated from the toxicological experiments will be used to extrapolate to the required level of sensitivity of the method using appropriate confidence interval techniques in accordance with the concepts underlying the Mantel-Bryan procedure discussed below. Where such extrapolation is not scientifically appropriate, e.g., if no dose-response slope can be estimated from the data, other conservative methods will be invoked to determine an appropriate safety margin based on a thorough evaluation of the quality of the experiments, their rigor as predictive tests and the nature and significance of the observed biological effects.

Where tests for carcinogenicity are required for a compound there are two basic objectives of the tests. The first is to determine whether or not the compound and/or its metabolites is a carcinogen. The second is to determine the relative potency of the compound and/or its metabolites with respect to both its carcinogenic and its noncarcinogenic but toxic effects, through appropriate oral dose-response experiments. Test systems will be selected which maximize sensitivity to detect a minimal dose which induces a carcinogenic effect. These systems will include a sufficiently stable control population to avoid false-positive indications of carcinogenesis.

There is a general lack of agreement within the scientific community regarding appropriate protocols for determining the dose-response relationship of carcinogenic compounds. Until they are revised, the guidelines for protocols set out by the Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides (Toxicology and Applied Pharmacology Vol. 20, pp 419–438, 1971) will be followed by the Food and Drug Administration.

If the results of the test for carcinogenicity establish that the compound or its metabolites will induce cancer in test animals, the required sensitivity of the regulatory assay method will be determined based on the Mantel-Bryan procedure described in the article entitled "Safety" Testing of Carcinogenic Agents (Journal of the National Cancer Institute, Vol. 27, pp 455–470, 1961). However, rather than assuming a dose-response relationship with a slope of one, as suggested in the reference, experimental data obtained from the carcinogenicity studies will be used to obtain a statistical estimate of the slope of the dose-response relationship. The lower 90 percent confidence limit of the estimated slope will be used for extrapolation to the required level of sensitivity of the regulatory assay method. If the data indicate that some linearizing transformation other than the probit-log transformation used in the modified Mantel-Bryan procedure better describes the observed response and has a biological rationale, then this other linearizing transformation may be used for such extrapolation. Examples of the application of this technique are given in the above reference.

Absolute safety can never be conclusively demonstrated experimentally. The level defined by the Mantel-Bryan procedure is an arbitrary but conservative level of maximum exposure resulting in a minimal probability of risk to an individual (e.g., 1/100,000,000), under those exposure conditions of the basic animal studies. Such test conditions generally involve continuous daily lifetime exposure to the compound in question. In contrast, many types of foods are consumed only intermittently, e.g., turkey or broiler kidneys, and therefore any drug residues contained in such foods will be consumed only intermittently. If the same procedure was used to determine the level of exposure for turkey kidneys as was used to determine the level of exposure for foods consumed more frequently, such as beef muscle, the population would not be equally protected in both situations. Consequently, it will be necessary to adjust the procedure for establishing the exposure level to account for usual as well as specific human consumption patterns. Any such adjustments initially will be made on a conservative basis. These adjustments will take into consideration the consumption expected by those who consume the greatest amounts of food, not the average consumption of the food. More definitive information is being complied on food consumption patterns by the Food and Drug Administration, and this information will be used to arrive at more refined adjustments as it becomes available.

It will also be necessary to modify the procedure for establishing the exposure level to account for drug usage, patterns, e.g., the administration of a drug in the treatment of diseased animals. As with consumption patterns, justified modifications will be made on a conservative basis. If a disease has a maximum incidence of 10 percent, then no more than 10 percent of the marketed animals would have been treated with the drug. Under these conditions, the probability of continuous daily exposure for an individual consumer could be very conservatively estimated as 0.10. In this situation, the true probability of risk for the individual consumer would then equal the probability of individual risk under conditions of continuous daily exposure to the drug multiplied by the probability of an individual actually experiencing continuous daily exposure to the drug. If a true exposure of 1/100,000,000 were deemed acceptable for an individual on the basis of risk-benefit considerations, this value could be held constant by assuming a continuous exposure risk of 1/10,000,000 (1/100,000,000=1/10,000,000 X 0.10) in the estimate of the Mantel-Bryan level. The true individual consumer risk would remain at 1/100,000,000 since the consumer is only intermittently exposed to residues of the compound in food.

The maximum level of exposure as estimated above, after standard adjustment for the differences between daily food intake per unit of body weight of the laboratory animal as compared with man, will be the required sensitivity of the assay method for a compound. In the event that both non-carcinogenic harmful effects and carcinogenic effects are observed during testing, the lowest level for the regulatory assay sensitivity as determined for the different effects will be adopted.

Withdrawal or post-medication periods for exogenous compounds shall be based on data obtained from tissue depletion studies. The compound must be administered to test animals for a sufficient time for concentration equilibrium to be achieved. On the basis of the developed assay and/or other suitable methods, a determination must be made as to the time when tissue levels of the parent compound and/or its metabolites and/or any affected endogenous compounds are below the required level of sensitivity for the regulatory assay method.

The withdrawal period shall be the longer of: (1) The number of days for tissue levels to be depleted to less than the maximum level of exposure extrapolated by the modified Mantel-Bryan procedure plus a safety factor to account for animal to animal variation (as determined by appropriate confidence interval techniques) or (2) the number of days for any affected endogenous compound to return to normal levels plus a safety factor to account for animal to animal variation. (The normal level of the affected endogenous compound will be established as described below for endogenous compounds.) For example, if excretion data indicate that the average depletion time for an exogenous compound is 72 hours with a safety factor of 27 hours, the withdrawal period becomes (72 hours+27 hours) = 24 hours or, after

01143

rounding upward, 5 days. Current livestock management techniques must be considered in establishing the withdrawal period and may necessitate the lengthening of this period.

The provisions of the proposed new regulation govern the required level of sensitivity of the regulatory assay method for those compounds for which a zero tolerance (no residue) is established. If a regulatory assay method of lower sensitivity is later developed and validated, however, the Commissioner will adopt that more sensitive method and publish it in the FEDERAL REGISTER, even though its development was not required under the law.

ENDOGENOUS COMPOUNDS

It is proposed that animals shown to contain tissue levels of endogenous compounds above the normal due to the administration of such compounds will not be permitted to be marketed for human consumption. Thus, neither tests for carcinogenicity nor standard toxicity testing will be required for endogenous compounds.

Naturally occurring (background) tissue levels of endogenous compounds and/or their metabolites and/or other related endogenous compounds in the target species must be determined in studies designed to show the effect of geographical location, stage of estrus, age, etc., on normal animals receiving no external source of the endogenous compound. The tissue distribution of the levels of the compound and/or its metabolites and/or other related endogenous compounds will be estimated from these studies. This distribution will be used to establish the required sensitivity of the regulatory assay method. The required sensitivity will be that level of the tissue distribution which is exceeded by only one percent of the normal animals. Tissue samples from animals at slaughter will be considered suspect if a level is found above normal background. For example, if 99.0 percent of background tissue levels for a parent endogenous compound and/or its metabolites and/or other related endogenous compounds are below 16 ppt., then a tissue level greater than 16 ppt shall be considered suspect. The final determination with respect to regulatory action will be based on a field investigation to determine if the observed value was due to a misuse of the compound or if it was due to normal biological variability.

Withdrawal periods following the last dosage for endogenous compounds shall be established based on the time required for the level of the parent compound and/or its metabolites and/or other related endogenous compounds in the tissue to return to the median background level of contemporary controls. The maximum approvable level of the compound shall be administered to target animals for a period of time sufficient to establish equilibrium in tissues. The number of days required for tissue levels of any affected endogenous compounds to return to the median background level plus a safety factor to account for animal to animal variation (as determined by appropriate confidence interval techniques) shall be used to establish the required withdrawal period. Current livestock management techniques must be considered in establishing the withdrawal period and may necessitate the lengthening of this period.

ASSAY EVALUATION CRITERIA

Prior to approval, the accuracy and reliability of the regulatory assay must be determined by validation of the method in appropriate Food and Drug Administration laboratories and other laboratories. The objectives of the validation will be to determine the feasibility, specificity, accuracy, and precision of the method (including a determination of the amounts recovered as well as an estimation of the variation associated with the recovered amounts).

Prior to submission of a method for evaluation and subsequent validation, it is recommended that the method be reviewed and tested, both qualitatively and quantitatively, by independent laboratories. This evaluation should fulfill the objectives of the validation as listed above.

The required sensitivity of the regulatory assay method as previously defined will be the regulatory action level and will be published in the FEDERAL REGISTER. Since any "positive" finding reported at a level lower than the published level of sensitivity may actually be a false positive, regulatory action will be taken only at or above the published level. This is necessary in order to assure that a residue is in fact a true positive. In the past the lack of such a procedure has led to finding violative samples in one laboratory which could not be confirmed in a second laboratory.

The assay method will be published or referenced in the FEDERAL REGISTER and will include a definition of the response criteria unique for each method which represents a reliable positive finding based on the validation studies. The criteria will take into account adjustments based on the accuracy and precision of the method. If the method is not specific for the identification of the compound or there are reasons to suspect the occurrence of false positives due to interference, a practical confirmatory test must be provided which will identify the residue at the level of sensitivity required.

In summary, the development and validation of a regulatory assay method for monitoring purposes must consider the following criteria:

1. The method must be capable of reproducibly extracting, at the required level of sensitivity, the significant compounds from target tissues obtained from treated animals as well as from tissues containing known added amounts of the compounds.

2. The method must be capable of measuring residues with a sufficient degree of specificity, precision, and accuracy to preclude the occurrence of false negatives or false positives.

3. The equipment, reagents and compounds used in the assay must be commercially available. Any required specialization in terms of equipment or personnel must be consistent with that normally available in a modern well-equipped analytical control laboratory.

4. The time required for completion of the assay must not be so excessive as to delay regulatory action, when necessary.

5. The assay must offer minimal hazard in the laboratory.

It is proposed that the requirements contained in this regulation will be applicable to all NADA's and supplemental NADA's approved by the Food and Drug Administration after the effective date of the new regulation. In determining the applicability of the provisions of the regulation to already-existing new animal drug approvals, the Commissioner will first determine those drugs for which a zero residue requirement now exists but for which a finite or negligible residue should instead be permitted. The Commissioner recognizes that many of these zero tolerances were established several years ago, at a time when detection methodology was substantially less sensitive and the available toxicology information was not as extensive. For some of these zero tolerances, it may now be possible and consistent with protection of the public health, to establish a finite or negligible residue. Where a finite or negligible residue is established on the basis of adequate safety data, the provisions of the new regulation will not be applicable.

Where a zero tolerance is deemed necessary, either because of a determination of carcinogenicity or because the compound is a suspect carcinogen or is otherwise sufficiently toxic that a determination of a safe level of residue in human food cannot be made at this time, the provisions of the new regulation will be applicable. The Commissioner recognizes that these new requirements cannot be imposed immediately. Accordingly, a determination will be made with respect to each drug as to a reasonable amount of time within which compliance will be permitted. In those instances in which the Commissioner concludes that a health hazard may exist, or where there is a failure to undertake the requisitie studies, the Commissioner will proceed immediately to withdraw approval of the drug. Hence, the above approach will permit a reasonable transition to the new requirements without compromising the public health or disrupting the use of drugs for which there is no known health hazard.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 402, 403, 409, 512, 701(a), 706, 52 Stat. 1046–1048, 1055, 72 Stat. 1785–1788 as amended, 74 Stat. 399–404, 82 Stat. 343–351; U.S.C. 342, 343, 348, 706, 360b, 371(a), 376), and under authority delegated to the Commissioner (21 CFR

01144

2.120), it is proposed that Part 135 be amended by adding the following new section:

§ 135.38 Compounds used in food-producing animals; procedures for determining the acceptability of assay methods used for assuring the absence of residues in edible products of such animals.

(a) The act provides that feed and drugs intended for animals shall be safe, that food produced from animals shall be safe, and that any compound administered to a food-producing animal which is found to induce cancer when ingested by man or animal is prohibited from the food supply, unless it can be determined by methods of examination prescribed or approved by the Secretary by regulation, that no residues of any such compound are found in the food produced from such animals under conditions of use reasonably certain to be followed in practice. Petitions for use of a compound in food-producing animals shall include data for determining the absence of residues of any unsafe compounds in the food produced from such animals. The provisions of this section shall determine the required level of sensitivity of the regulatory assay method for any compound for which the Commissioner of Food and Drugs has established a zero tolerance (no residue) in food.

(b) Exogenous compounds, defined as those compounds which are not produced by the normal animal and are not required for normal animal body function, are subject to the following requirements:

(1) Metabolism studies shall be conducted in the target species to identify and quantify metabolites of the parent compound and the concentrations of the compound and its metabolites in specific tissues ("tissues" to include milk and eggs, if applicable). The effect of the exogenous compound on tissue levels of related endogenous compounds also shall be determined.

(2) Degradation of the compound and/or its metabolites during the period of time after slaughter that edible tissue would normally be held under storage conditions and the impact of cooking on the compound and/or its metabolites in question shall be determined.

(3) Determination of whether an exogenous compound and/or its metabolites shall be subjected to appropriate testing for carcinogenicity will be based on the results of the metabolism studies, standard toxicity testing, structural relationships of the compound and/or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended use patterns of the compounds.

(4) If it is determined that carcinogenicity tests are not required or if the results of carcinogenic testing are negative, consideration for approval shall be based on standard toxicological procedures. These procedures shall include in addition to subacute studies in a minimum of two species, such studies as a multi-generation reproduction studies, teratology and any other special studies which may be indicated from the nature of the biological action of the compound, including lifetime studies. These studies shall involve collection of data from appropriately designed dose-response experiments that demonstrate a "maximum no harmful effect level" as well as a "minimum harmful effect level" in appropriate animal species.

(i) Where a finite or negligible residue of the parent compound and/or its metabolites is determined to be safe in food, the required level of sensitivity of the regulatory assay method will be the level of the tolerance published in the FEDERAL REGISTER and the remaining provisions of this paragraph shall be inapplicable.

(ii) Where no residue of the compound and/or its metabolites is determined to be safe in food, the dose-response slope estimated from the toxicological experiments will be used to extrapolate to the required level of sensitivity of the method using appropriate confidence interval techniques in accordance with the concepts underlying the Mantel-Bryan procedure described in paragraph (b)(6) of this section. Where such extrapolation is not scientifically appropriate, e.g., if no dose-response slope can be estimated from the data, other conservative methods shall be invoked to determine an appropriate safety margin based on a thorough evaluation of the quality of the experiments, their rigor as predictive tests and the nature and significance of the observed biological effects.

(5) If it is determined that testing for carcinogenicity is required, test procedures shall be used which maximize sensitivity to detect a minimal dose which induces a carcinogenic effect and with a sufficiently stable control population to avoid false positive indications of carcinogenesis. Appropriate dose-response experiments shall be conducted to (i) clearly establish whether or not the compound and/or its metabolites are carcinogens, and (ii) determine the relative potency of the compound and/or its metabolites with respect to both its carcinogenic and its other toxic effects.

(6) If it is determined that the compound is carcinogenic, the required sensitivity of the regulatory assay method shall be established according to a modification of the Mantel-Bryan procedure. (Mantel, N. and W. R. Bryan, "Safety" Testing of Carcinogenic Agents, Journal of the National Cancer Institute, Vol. 27, pp. 455–470, 1961).[1] This modification shall consist of using the lower 90 percent confidence limit of the experimentally determined dose-response slope from the carcinogenicity studies for extrapolation to a maximum exposure level with appropriate adjustments to account for drug usage and human consumption patterns and for the differences between daily food intake per unit of body weight of the laboratory animal and of man. (i) If the data indicate that some linearizing transformation other than the probit-log transformation used in the modified Mantel-Bryan procedure better describes the observed response and has a biological rationale, then this other linearizing transformation will be used for the extrapolation. (ii) In the event that both significant noncarcinogenic harmful effects and carcinogenic effects are observed during testing, the lowest level for the regulatory assay sensitivity as determined for the different effects shall be adopted.

(7) The sensitivity of the regulatory assay method as defined above, the method, and a definition of the criteria used to establish a reliable positive finding shall be published in the FEDERAL REGISTER.

(8) The withdrawal period for the compound shall be based, using the regulatory assay method and/or other suitable methods, on the time required after the last dosage for tissue levels of the parent compound and/or its metabolites and/or any affected endogenous compounds to fall below the required regulatory assay sensitivity.

(9) The withdrawal period shall be the longer of either (i) the number of days required for tissue levels to be depleted to less than the maximum exposure level plus a safety factor to account for animal to animal variation as determined by appropriate confidence interval techniques or (ii) the number of days required for any affected endogenous compound to return to a normal level plus a safety factor to account for animal to animal variation. Current livestock management techniques may justify a longer withdrawal period. The normal level of any affected endogenous compound shall be established as described in paragraph (c) of this section.

(10) Based on tissue depletion studies and animal management practices, conditions of use that are reasonably certain to be followed in practice shall be specified for the compounds so that, if followed, they assure that no residue shall occur in food produced from treated animals.

(11) Notwithstanding a determination pursuant to this paragraph of the required level of sensitivity of the regulatory assay method, if a regulatory assay method of lower sensitivity is later developed and validated the Commissioner will adopt that more sensitive method and publish it in the FEDERAL REGISTER even though its development was not required.

(c) Endogenous compounds, defined as those compounds which are present in and are produced by the normal animal and are not required from an external source, are subject to the following requirements:

[1] Copies may be obtained from: Director, Division of Nutritional Sciences (VM–100), Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

(1) Metabolism studies shall be conducted in the target species to identify and quantify the metabolites of the parent compound and the concentrations of the compound and its metabolites in specific tissues ("tissues" include milk and eggs, if applicable). The effect of the endogenous compound on tissue levels of related endogenous compounds also shall be determined.

(2) Degradation of the compound and/or its metabolites during the period of time after slaughter that the edible tissue would normally be held under storage conditions and the impact of cooking on the compounds and/or its metabolites in question shall be determined.

(3) Animals containing tissue levels of endogenous compounds above the normal due to the administration of endogenous compounds may not be marketed for human consumption. Thus, neither tests for carcinogenicity nor standard toxicity testing shall be required for endogenous compounds.

(4) The naturally occurring or background tissue levels of endogenous compounds and/or their metabolites and/or other related endogenous compounds in the target species shall be determined in studies designed to show the effect of geographical location, stage of estrus, age, etc., on normal animals receiving no external source of the endogenous compound. The tissue distribution will be used to establish the required sensitivity of the regulatory assay method. The required sensitivity of the regulatory assay method will be that value of the distribution which is exceeded by only one percent of the normal animals.

(5) The sensitivity of the regulatory assay method as defined above, the method, and a definition of the criteria used to establish a reliable positive finding shall be published in the FEDERAL REGISTER.

(6) The withdrawal period for the compound shall be based using the regulatory assay method and/or other suitable methods, on the time required after the last dosage for the tissue levels of the parent compound and/or its metabolites and or any affected other related endogenous compounds to return to the median background level of contemporary controls. The withdrawal period shall be the number of days required for tissue levels of any affected endogenous compounds to return to the median background level plus a safety factor to account for animal to animal variation as determined by appropriate confiidence interval techniques. Current livestock management techniques may justify a longer withdrawal period.

(7) The characteristics of the distribution of tissue levels of the compound normally found in animals not exposed to external sources of the compound and the specified conditions of use shall be published in the FEDERAL REGISTER as part of the approval of any endogenous drug compound.

(8) Based on tissue depletion studies and animal management practices, a withdrawal period and conditions of use that are reasonably certain to be followed in practice shall be specified for the compound so that, if followed, they assure that no residue shall occur in excess of the established normal level in food from untreated animals.

(d) Prior to approval, the adequacy of the regulatory assay method shall be determined by validation of the method in appropriate Food and Drug Administration laboratories and other laboratories. The validation shall determine the feasibility, specificity, accuracy, and precision of the method. This validation of an assay method used for regulatory purposes shall be based on the following criteria:

(1) The method shall be capable of reproducibly extracting, at the required level of sensitivity, the significant compounds from target tissues obtained from treated animals, as well as from tissues containing known added amounts of the compounds.

(2) The method shall be capable of measuring residues with a sufficient degree of specificity, precision, and accuracy to preclude the occurrence of false negatives or false positives.

(3) The equipment, reagents and compounds used in the assay shall be commercially available. Any required specialization in terms of equipment or personnel shall be consistent with that normally available in a modern well-equipped analytical control laboratory.

(4) The time required for completion of the assay shall not be so excessive as to delay regulatory action.

(5) The assay shall offer minimal hazard in the laboratory.

(e) After publication in the FEDERAL REGISTER of an assay method in accordance with paragraphs (b) through (d) of this section, compliance shall be determined as follows:

(1) Samples of the food produced from appropriate animals will be routinely collected and evaluated using the regulatory assay method(s).

(2) Any sample subject to paragraph (b) of this section yielding a residue of the compound at or above the published level of sensitivity of the method will be liable to regulatory action.

(3) Any sample subject to paragraph (c) of this section yielding a residue of the compound at or above the published level of sensitivity of the method will be subject to investigation. Any such residue which is determined to be the result of improper use of the compound will be liable to regulatory action.

(4) No regulatory action may be based on the measurement of a value which is below the established level of sensitivity of the approved regulatory assay method(s) as published in the FEDERAL REGISTER.

(f) The provisions of this section shall be applicable to all new animal drug applications, including supplements, approved by the Food and Drug Administration subsequent to the effective date of the final regulation, except that supplemental applications meeting the requirements of § 135.13a(d) or that in the opinion of the Commissioner otherwise protect the public health will be permitted to be put into effect in accordance with § 135.13a(e) through (k).

(g) The provisions of this section shall be applicable to existing approvals of new animal drugs in accordance with the following priorities:

(1) The Commissioner will review existing zero tolerances (no residues) to determine whether the drugs involved should be the subject of finite or negligible residues. Those drugs for which finite or negligible residues are established are not subject to the provisions of paragraphs (b) or (c) of this section.

(2) Those drugs for which the Commissioner has determined the appropriateness of a zero tolerance (no residue) will be the subject of a notice published in the FEDERAL REGISTER or a letter to every holder of a new animal drug application establishing a time within which the provisions of this section shall be satisfied. Notices already published in the FEDERAL REGISTER and letters already sent by the Food and Drug Administration requiring additional studies and/or a more sensitive regulatory assay method for a drug subject to a zero tolerance shall remain in effect, and the provisions of this section shall be used in determining compliance with the requirements of the act pursuant to those notices and letters. The Commissioner will immediately proceed to withdraw approval of any drug on the basis of data or information indicating a health hazard or a failure to undertake studies necessary to comply with the provisions of this section.

Interested persons may, on or before September 17, 1973, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be viewed in the above office during working hours, Monday through Friday.

Dated: July 13, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-14746 Filed 7-18-73;8:45 am]

Social Security Administration

[20 CFR Part 405]

[Reg. No. 5]

FEDERAL HEALTH INSURANCE FOR THE AGED AND DISABLED

Payment for Services of Physicians in Teaching Hospitals, for Physician Costs to Hospitals and Medical Schools, and for Volunteer Services

Notice is hereby given, pursuant to the Administrative Procedure Act (5 U.S.C. 552 et seq.) that the amended regulations set forth in tentative form below are proposed by the Acting Commissioner of Social Security, with the approval of

01146

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER A—GENERAL

SUBCHAPTER E—ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS

[Docket No. 77N-0026]

CHEMICAL COMPOUNDS IN FOOD-PRODUCING ANIMALS

Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Edible Products of Animals

The Food and Drug Administration (FDA) is establishing procedures and minimum criteria to ensure the absence of carcinogenic residues in edible products derived from food-producing animals that are administered drugs, food additives, or color additives. These regulations set forth below provide an operational definition of the no-residue requirement of the so-called "DES proviso" to the anticancer clauses, sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B), of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(c)(3)(A), 360b(d)(1)(H), and 376(b)(5)(B)). The regulations also establish criteria for acceptance of assay methods and procedures for establishing suitable post-administration withdrawal periods to prevent the occurrence of carcinogenic residues in edible products. The regulations shall become effective on March 21, 1977.

Prior to July 19, 1973, FDA had applied the proviso to the anticancer clauses of the act on a case-by-case basis, without published criteria. The Commissioner of Food and Drugs concluded that it was appropriate and necessary to establish such criteria and procedures for their application through rule making in order to permit public discussion of the scientific, legal, and policy issues involved. Accordingly, the Commissioner issued these regulations as a proposal, published in the FEDERAL REGISTER of July 19, 1973 (38 FR 19226), and afforded 60 days for public comment.

Forty-six comments on the proposal were received. These were submitted by scientists affiliated with consumer groups, universities, scientific societies, State and Federal agencies, trade associations, and affected manufacturers, and some from nonaffiliated individuals. Many comments revealed sharp divergence of opinion concerning FDA's interpretation of the proviso to the anticancer clauses of the act. For this reason, the Commissioner has set forth, initially, the legal and scientific rationale for these final regulations. Specific comments are described and discussed later in the preamble in connection with the provisions of the regulations to which they relate.

I. INTRODUCTION

A. STATUTORY BACKGROUND

Section 409 of the Federal Food, Drug, and Cosmetic Act establishes criteria and prescribes procedures for the approval of food additives that have been shown to be safe. As enacted in 1958, the anticancer (or so-called Delaney) clause of section 409 flatly proscribed the approval of any additive that "is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *." As applied to additives added directly to human food, this language has remained unchanged. Accordingly, as a legal matter, section 409 precludes a finding by FDA that a direct food additive that has been shown to cause cancer in laboratory animals (or, of course, in man) can be safely added to food, in any amount, for any purpose. Section 706 of the act similarly prohibits the approval of any carcinogenic color additive.

The use of chemical compounds as additives to the feed of animals or as animal drugs has posed more complex problems. The act requires that compounds administered to animals as food additives, color additives, or animal drugs be shown to be safe for use. Under section 201(u) of the act (21 U.S.C. 321(u)), the term "safe" clearly embraces the health of man, as well as the health of the animals to which such compounds are given. Thus, in evaluating the safety compounds to be administered to animals raised or maintained for production of food for man, such as cattle, swine, and poultry, Congress has from the beginning recognized that consideration had to be given to the safety of possible residues of the compounds in the products of animals that become sources of food for man, i.e., meat, milk, and eggs.

Prior to 1962, the anticancer clauses in section 409 and section 706 did not distinguish between compounds added directly to human food and compounds that might indirectly enter human food through administration, as feed additives or drugs, to food-producing animals. The act was interpreted as forbidding FDA to approve the use of a carcinogenic animal drug whether or not the compounds might leave any residues in the edible tissues of the animal. However, Congress modified this flat prohibition in 1962 as part of the Drug Amendments of 1962, to focus on the likelihood that a compound would produce detectable residues. Section 409(c)(3)(A) now reads:

> * * * [N]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal, except that this proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (1) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (2) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g)) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal * * *

Modification of the effect of the anticancer clause of section 409 was first suggested during congressional consideration of the Color Additive Amendments of 1960. In May 1960, the then-Secretary of Health, Education, and Welfare urged Congress to modify the act, explaining:

> There is * * * one respect to which the anticancer proviso has proved to be needlessly stringent as applied to the use of additives in animal feed. For example, in the case of various animals raised for food production, certain drugs are used in animal feed which will leave no residue in the animal after slaughter or in any food product (such as milk or eggs) obtained from the living animal, and which are therefore perfectly safe for man. If this is demonstrated with respect to any particular additive intended for animal feed, and the additive will not adversely affect the animal itself during its expected or intended life cycle, we can see no reason for not permitting such a use of an additive which could be highly useful and beneficial in the raising of animals for food * * *.
>
> We therefore have included in the enclosed draft bill an amendment to permit use of an additive in animal feed under the above-mentioned conditions.
>
> * * * * *
>
> [U]nder the amendment, the assay methods applicable in determining whether there will be a residue shall be those prescribed or approved by us by regulations. This will give reasonable certainty in that regard, although, of course, such regulations may from time to time be changed as new scientific developments demonstrate a need for change. It should be clearly understood that the industry still would have the responsibility of developing adequate analytical methods for detecting residues and furnishing them to the Government with a petition for approval of an additive. H.R. Rep. No. 2664, 86th Cong., 2d Sess. (1960).

The amendments proposed by the Department were not included in the color additive legislation. During the following 2 years, however, concern continued to be expressed about application of the anticancer clause in section 409. As a result, legislation similar to that earlier recommended by the Department of Health, Education, and Welfare was introduced in 1962. The House Committee on Interstate and Foreign Commerce ultimately included modifications of the anticancer clause in its report on the Drug Amendments of 1962, with the following explanation:

> The committee amended the anticancer clause of the food additives amendment and the color additive amendment of the Federal Food, Drug, and Cosmetic Act by making this clause inapplicable to chemicals such as veterinary drugs when used in feed for food-producing animals if the Secretary finds (1) that under the conditions of use and feeding specified in the proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (2) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations) in any edible portion of the animal

01147

after slaughter or in any food such as milk or eggs yielded by or derived from the living animal. H.R. Rep. No. 2464, 87th Cong., 2d Sess. (1962).

Although controversial, these amendments were agreed to by the full House of Representatives. The Senate accepted the House-passed modifications of the anticancer clauses in conference (H.R. Rep. No. 2526, 87th Cong., 2d Sess. (1962)).

Beginning in 1962, efforts were also made in Congress to consolidate the various provisions of the law applicable to animal drugs under the new drug, food additive, and antibiotic sections of the statute, with the objectives of clarifying the applicable requirements and expediting approvals of new animal drugs. No attempt was made to reopen the issue of the anticancer clause, however, and neither the committee reports nor the floor debates in the resulting legislation mentioned the anticancer clause which precluded approval of a new animal drug if:

* * * such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h)), in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals * * *. (21 U.S.C. 360b(d)(1)(H).)

The legislation was enacted without controversy as the Animal Drug Amendments of 1968, and without evident congressional desire to alter the anticancer clauses, as modified in 1962 for animal drugs.

B. STATUTORY INTERPRETATION

The enactment in 1962 of the so-called DES proviso to the Delaney anticancer clause has been a source of continuing controversy. There has not been unanimity on the proper interpretation of Congress' action, and the legislative history of the proviso, summarized above, does not lay to rest all doubts.

Two interpretations of the proviso are, in theory, possible. The first interpretation, which in the Commissioner's judgment is the less probable, is that Congress intended to allow FDA to approve the use of a carcinogenic compound in food-producing animals only if it could be absolutely positive that no traces whatever—no matter how small—would remain in edible tissues.

This interpretation presents several difficulties, all stemming from the fact that any introduction of a compound (whether or not carcinogenic) is likely to leave minute residues in edible tissues that are below the level of detection of any known or likely to be developed method of analysis (assay). It is a fundamental fact of analytical science that for every assay developed to measure the concentration of a chemical compound in a medium (in this case, a residue in an edible tissue, there is some lowest concentration or level of such compound below which the assay will not yield an interpretable result. If, for example, an assay measures a particular compound in muscle tissue (an edible tissue), and the assay has been shown to have a lowest limit of measurement of one part per billion (1 ppb—one part compound in one billion parts tissue on a weight basis, such as 1 nanogram of compound per 1 gram of tissue), examination of muscle tissue using this assay will reveal that the compound is present only if its concentration in muscle tissue is 1 ppb or higher. If the compound is present in the tissue at levels below 1 ppb, use of the assay will yield no interpretable result. Thus, the assay cannot distinguish between muscle tissues containing the compound at levels below 1 ppb and muscle tissues from which the compound is absent in the absolute sense of the term.

Although different assays may have different lowest limits of measurement, all assays are subject to the same limitation. Thus, when a tissue is examined with an assay having a lowest limit of measurement of 1 ppb and no interpretable response is observed, the analyst can only conclude that the compound under analysis is not present at levels of 1 ppb and above. It can never be concluded that the compound is "not present" in the absolute sense. It is thus impossible to determine the conditions under which edible tissues derived from food-producing animals that have received a carcinogen will contain no residue if the phrase "no residue" is to be interpreted literally. Accordingly, this first possible interpretation of the DES proviso would not permit the approval of any animal drug known to be carcinogenic because the Commissioner could never find that no trace whatever would remain in the edible tissues of the animals to which the compound was administered.

This interpretation would thus render the DES proviso a "Catch-22." The proviso would permit the approval of carcinogenic drugs for animals if the Commissioner could be certain that no residues whatever would remain, but since he would only conclude that some trace might well remain, no such drug could ever be approved. This seems, at the very least, an improbable interpretation of an amendment Congress enacted precisely because it wanted to relieve animal drugs from the rigid strictures of the anticancer clauses.

Furthermore, this interpretation is difficult to reconcile with the language of the DES exception, which specifies that "no residue" may be "found (by methods of examination prescribed or approved by the Secretary * * *) in any edible portion of such animals * * *." This language conspicuously avoids such words as "occur" or "remain," and instead emphasizes detectability. Moreover, the same proviso refers to "conditions of use * * * reasonably certain to be followed in practice," suggesting a congressional recognition that the occurrence of some residues, i.e., residues resulting from unforeseeable misuse, might not require disapproval of a compound even if they were detected.

A second, and in the Commissioner's view more plausible, interpretation of the DES proviso accepts the words of the amendment and focuses on the language previously quoted: "no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations * * *." Under this interpretation, an animal drug that is carcinogenic may be approved for use in animals if examination of edible tissues by an assay approved by FDA reveals no residues.

This in essence is the interpretation that FDA has followed since the passage of the DES proviso: The agency has approved carcinogenic compounds for use in animal feed or as animal drugs on the basis of assays capable of measuring prescribed levels of residues. However, the agency has not previously attempted to define and explain the criteria it employs in evaluating assays submitted in support of approval of animal drugs, feed additives, and color additives. That is the purpose of this document.

The Commissioner believes that the criteria to be applied in evaluating assays for residues of carcinogenic compounds in the edible tissue of food animals must further the congressional objective of minimizing public exposure to carcinogenic compounds, without nullifying the decision reflected in the DES proviso, which the first interpretation of the proviso would do. As explained more fully below, the criteria set forth in these regulations for the evaluation of assays for carcinogenic residues are minimum requirements. They are designed to identify assays that are (1) reliable and practical for use by a regulatory agency and (2) capable of measuring residues at levels that have been determined, on the basis of animal toxicity tests, to present no significant increase in human risk of cancer. An assay that does not meet both criteria cannot be approved. The Commissioner recognizes that for some compounds currently in use no reliable and practical assay capable of sufficiently low limits of measurement now exists, and that approval of their continued use must be reexamined.

The Commissioner further believes that the policy embodied in the anticancer clauses requires application of a third criterion to the evaluation of assays: The agency therefore will insist that of the available assays, the one approved for controlling carcinogenic residues must be the one having the lowest limit of reliable measurement and capable of satisfying the other two criteria. This means that, as new practical assays capable of reliably measuring lower levels of residues become available, approved compounds will be controlled with such assays and petitioners will be required to make any modifications in the conditions of use of a compound necessary to prevent residues from occurring.

01148

The Commissioner recognizes that this third criterion may lead to the withdrawal of approval of some compounds because they cannot be used without detection by newer assays. (This prospect is in part theoretical, however, because the other minimum criteria defined in this regulation demand a low limit of measurement for assays that for many compounds is at or below the lower limits of present technology.) Any other posture, however, would place FDA in the position of approving the use of carcinogenic compounds that could be measured by new, practical assays capable of reliably measuring lower levels of residues.

It is, of course, also true that the criteria outlined in these regulations will sometimes permit the approval, for use in animal feed or as animal drugs, of carcinogenic compounds that are likely to leave miniscule residues below the lowest level of reliable measurement of any assay that meets the other criteria herein set forth. This, however, is the result of congressional enactment of the DES proviso. Moreover, this result makes sense in practical terms, for a regulatory agency cannot effectively control residues—of any compound—that are so small that they escape measurement by every current assay, simply on the assumption that such residues must be occurring.

In sum, the interpretation adopted in these regulations is reconcilable with both the purpose and language of the DES proviso, and will further the congressional objective of minimizing public exposure to residues of carcinogenic compounds.

C. OVERVIEW OF THE REGULATION

The proviso to the anticancer clauses allows the approval of the use of carcinogens in food-producing animals if, under conditions of use "reasonably certain to be followed in practice," no residue is found by an (assay) prescribed or approved by the Secretary. To assure protection of the public in a manner consistent with the anticancer provisions of the act, the Commissioner must establish criteria for approval of assays to include, among other things, a required lowest limit of measurement.

Accordingly, these regulations establish criteria for accepting assays used to measure carcinogenic residues in edible tissues of food-producing animals which have been administered carcinogens. Such criteria cover assay attributes such as dependability, practicability, specificity, accuracy, and precision. Additionally, the regulations establish a specific criterion for the lowest limit of reliable measurement which an assay must meet, as a minimum, before it can be approved by the agency for the control of carcinogenic residues. This criterion for the required lowest limit of measurement of an assay derives from toxicological data obtained for carcinogenic residues and from an operational definition of the no-residue objective standard of the act. Only if an assay meeting the above criteria is available does the Commissioner have a mechanism to discriminate between tissues containing a residue and tissues containing no residue. Without such a monitoring mechanism, the commissioner has no way to determine if a carcinogenic drug or additive administered to a food-producing animal is or even can be used in compliance with the act.

In these regulations the Commissioner has established a rigorous premarket testing process for sponsored compounds intended for use in food-producing animals. The process treats all compounds initially as potential carcinogens and embodies conservative assumptions at each stage of the inquiry to determine the minimally acceptable lowest limit of reliable measurement for a regulatory assay. Because this minimally acceptable limit is determined by toxicity data, the Commissioner may conclude that an assay satisfying the requirements of the regulations is capable of demonstrating the absence of carcinogenic residues in food. By thus particularizing the statutory requirements, the Commissioner has established the basis for rejecting sponsored compounds which are claimed to satisfy the no-residue standard by other mechanisms.

1. *Fundamental questions.* For every drug or additive proposed for use in food-producing animals (hereinafter the sponsored compound), the Commissioner is required by the act to determine whether such sponsored compound can be used in ways which are safe for the animals to which the compound will be administered (target animals) and whether food (meat, milk, and eggs) derived from such animals (hereinafter edible tissues) will be safe for human consumption. The sponsor of such compound (hereinafter the petitioner) is therefore required to furnish the Commissioner the scientific and technological information necessary for such a determination; the Commissioner in turn is required by the act to determine on the basis of all available data whether, in actual practice, the sponsored compound can be used in compliance with the law.

Although a major obligation of a petitioner proposing the use in food-producing animals of a compound that is a carcinogen is the development of a practical and reliable assay capable of discriminating tissues containing residues from tissues free of such residues, as defined operationally, such as an assay cannot be developed in the absence of certain scientific and technological information whose nature is not strictly analytic.

Specifically, for every sponsored compound, several questions must be answered before assay development can be undertaken or compound approval considered:

(a) What is the chemical nature of the sponsored compound and how is it to be used?

(b) On the basis of preliminary toxicological and biochemical information, can it be concluded that the compound has the potential to contaminate human food (edible tissues) with residues of carcinogenic concern?

(c) If so, what is the chemical nature of the residues of the compound, in what tissues are they found, at what levels, and for what length of time?

(d) Is the sponsored compound or any of the residues it produces in edible tissue carcinogenic in experimental animals?

(e) If so, what level of residues can be operationally defined as satisfying the no residue requirement of the act?

(f) Can a reliable and practical assay be developed to measure the edible tissue residues at a level at least as low as that which operationally satisfies the no-residue requirement of the act?

(g) At what time after cessation of compound exposure do the edible tissues of exposed food-producing animals satisfy the no-residue requirement of the act, i.e., what is the necessary withdrawal time?

2. *Data collection process.* To provide answers to the preceding questions, a petitioner must gather pertinent scientific information, the nature of which is particularized below. These regulations establish the procedure for gathering and evaluating the requisite scientific information. The process is stepwise and evolutionary because the need, as well as ability, to proceed to the next step of data collection depends upon the results obtained at each preceding step. If the evaluation of the data collected at each step indicates that questions regarding residues of carcinogenic concern remain, the process of data collection must continue. If at some point in the process of data collection it can be decided that the sponsored compound presents no human risk of carcinogenesis, the sponsored compound shall be evaluated under the general food safety provisions of the act. In such a case, the compound may be assigned a safe tolerance level in human food if the petitioner provides the data necessary to establish that the compound can be used safely.

These regulations deal with carcinogenesis, which is a dominant concern in appraising the safety of any sponsored compound intended for use in food-producing animals. Nevertheless, each compound must also be evaluated for other potential adverse effects. Thus, for example, if the available information raises issues concerning the health of progeny, multigeneration studies of the sponsored compound and/or its residues shall be codesigned and conducted as a part of the process of data collection and evaluation.

If the Commissioner makes a threshold determination, based on (1) preliminary biochemical, chemical, toxicological and physiological data, and (2) proposed patterns of use, that a sponsored compound has the potential to contaminate food from food-producing animals with residues whose consumption would pose a human risk of carcinogenesis, the petitioner will be required to undertake the following six-step procedure for data collection and evaluation.

(a) A metabolic study in the target animals designed to identify edible tissue residues of carcinogenic concern.

01149

(b) A metabolic study of the sponsored compound in experimental animals designed to aid in assessing the carcinogenicity of residues that can not practicably be tested individually (so-called "intractable residue").

(c) Chronic toxicity testing to assess the carcinogenic potential of residues of the sponsored compound and to furnish data suitable for statistical treatment to permit the no-residue requirement of the act to be defined and implemented.

(d) A detailed metabolic study of the sponsored compound in target animals designed to identify a residue and tissue that can serve as indicators ("marker residue" and "target tissue") to determine whether the no-residue requirement of the act is satisfied.

(e) Development of a regulatory assay to measure the marker residue in the target tissue at and above the level established in step (d).

(f) Establishment of the premarketing withdrawal period required for the safe use of the sponsored compound.

Because the partial provisos to the anticancer clauses of the act, sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B), although varying slightly in their language, have a similar intent, the Commissioner has concluded that the criteria for their implementation should also be identical. To avoid needless repetition, however, where appropriate the Commissioner has used the language of section 512 of the act in discussing specific generic issues because the primary impact of these regulations will be on new animal drugs regulated under that section. The criteria set forth in these regulations shall, however, apply to all chemicals intended for use in food-producing animals, and the appropriate regulations will be amended to adopt these criteria by reference.

Since issuing the proposal under § 135.-38 (21 CFR 135.38), FDA has recodified all regulations applicable to animal products in Subchapter E of Title 21 of the Code of Federal Regulations to provide space for the orderly development of future regulations and to provide the public and other affected parties with regulations that are easy to find, read, and understand. For these reasons, the final order has subdivided the proposal into 10 individual regulations and established a new subpart in Part 500, Subpart E—Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Edible Products of Animals.

II. Threshold Assessment

In the 1973 notice of proposed rulemaking, the Commissioner proposed that carcinogenicity testing not be required for every sponsored compound. Rather, he concluded that the necessity for such testing will be dictated by an evaluation of the existing evidence from metabolic studies, standard toxicity testing, structural relationships of the sponsored compound and/or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended method of use of the sponsored compound.

Comments of two types were received on this feature of the proposal. The first suggested that extensive studies should be conducted for every sponsored compound to determine whether it is a carcinogen. One comment insisted that extensive carcinogenesis testing for every sponsored compound is the only accurate indicator of carcinogenic potential. Several contended that the criteria proposed for use in the threshold determination were too vague, and objected to the lack of explanation of how such criteria could be applied in practice.

Many other comments agreed with the Commissioner's proposal that extensive carcinogenicity testing should not be required for every sponsored compound. These comments recommended that the Commissioner review all available data pertaining to a sponsored compound before he concludes that the stepwise testing procedure set forth in the proposal and adopted in this regulation should be invoked.

When a petitioner initiates the process of gaining approval for use of a compound, information is provided to the agency on matters such as compound efficacy and its proposed patterns of use. Often a petitioner will also provide preliminary physiological, metabolic, or toxicological data derived from its own studies or from the scientific literature. At this juncture, the Commissioner believes it necessary that a threshold assessment be made, based on the available data, on the need to proceed to the first of the six steps of data collection required by these regulations. Because entry into the six steps of data collection requires that a petitioner undertake a series of very complex and costly experimental studies, imposing demands on the limited national resources available for determining the safety of chemicals entering the environment, the Commissioner concludes that it is not reasonable to demand such studies on a sponsored compound if the preliminary data available justified the judgment that public health can be protected without so proceeding.

Criteria for this threshold assessment cannot be elaborated in detail. The Commissioner must examine the available preliminary data, which may vary considerably in quality and content from one compound to the next, on a case-by-case basis and determine whether a sponsored compound has the potential to contaminate edible tissues with residues of carcinogenic concern. However, certain general characteristics of the compound shall always be considered in making the threshold assessment:

(1) Is the compound a known carcinogen or is it related, in a chemical or biological sense, to other known carcinogens?

(2) Is there an indication in preliminary toxicity studies that the sponsored compound may be carcinogenic?

(3) Does preliminary information on the fate of the compound in target animals indicate that, in combination with information on the proposed pattern of use, there is a high or low probability that residues can occur in edible tissues when such tissues become available as food?

In making a threshold assessment, the Commissioner may or may not have answers to these questions and, in some instances, may not need answers to all of them to make a decision. It will sometimes be obvious that the first step of the six-step process will have to be undertaken. In other cases, it will be equally clear that no such inquiry need be begun, and the compound can be evaluated under the general food safety provisions of the act. Finally, in some cases, available information will be so incomplete or ambiguous that a decision will be made to move to the first step to assure protection of public health. As will be shown later, it is possible that information developed in later steps may support or require revision of the threshold assessment that a compound had the potential to contaminate tissues with residues of carcinogenic concern, in which case the remaining steps of these regulations will not be required and evaluation will proceed under the general food safety sections of the act.

The following examples illustrate how a threshold assessment can be made:

Case I.—A drug is proposed for use in day-old chickens. Preliminary information indicates that:

(a) Neither chemical structure nor preliminary (short-term) toxicity testing raise a suspicion that the drug is a carcinogen.

(b) The drug is proposed for therapeutic use only in a single administration to day-old birds.

(c) The disease to be treated occurs infrequently.

(d) Preliminary metabolic data indicate accumulation of residues in kidney and no detectable residues in muscle.

(e) Residues deplete rapidly and none are detected many weeks before the chickens reach marketing weight.

If presented with the foregoing information, the Commissioner would see no justification for demanding that the petitioner proceed to the first step of these regulations which governs compounds having the potential to contaminate edible tissues with residues of carcinogenic concern. However, if the preliminary metabolic study in the example had been conducted with an assay having a lowest limit of reliable measurement of residues substantially higher than current technology can attain, the Commissioner would conclude that the available data were insufficient to justify a favorable threshold assessment about the sponsored compound, and the petitioner would be required to proceed to the first step of these regulations. It is precisely because of such contingencies that the Commissioner concludes that no more specific criteria for threshold assessment should be established by regulation.

Case II.—A drug having growth promoting properties is proposed for use in cattle. The preliminary information indicates that:

(a) The observed physiological activity of the drug in cattle indicates that it is

01150

in a class of other known carcinogens whose carcinogenic properties appear to be related to this particular physiological activity (i.e., the drug is a suspect carcinogen).

(b) The drug is used during a large fraction of the lifetime of the animal.

(c) The drug is likely to be widely used in animal husbandry.

(d) Preliminary metabolic data show that residues of the drug accumulate in muscle tissue (meat) and deplete very slowly. On the basis of such information, it is obvious that the Commissioner would have to require the petitioner to proceed to the first step of the required six-step process.

III. Metabolic Study in Target Animals To Identify Residues of Concern

A. Need to Identify Residues in Edible Tissue

Before any decision can be made concerning conditions of safe use of a sponsored compound, it is necessary to obtain information on the residues that occur in edible tissues when the compound is administered to the animals for which it is intended (target animals). Without such information, rational decisions about the human safety of edible tissues derived from treated animals are not possible.

A compound administered to an animal can be acted upon by the enzymatic systems or physiological fluids of the animal and new compounds (metabolites and degradation products of the sponsored compound) are produced in the process. Therefore, the sponsored compound is not the only tissue residue of concern. And sections 512(b)(7) and 512(d)(2) of the act explicitly require the Commissioner to consider the safety of any substance formed in or on food by a sponsored compound before approving its use.

Numerous comments were received on the proposal's requirement for metabolic studies. Several comments stated that there should be no attention paid to metabolites. Others contended that metabolism studies should not be routinely required, on the ground that the pathway of excretion is of no toxicological importance if all of the administered compound has been eliminated from the tissues of the target animal. Most comments recommended that a metabolism study should only be required to determine the major metabolites in the edible tissue of target animals, suggesting that the public health would not be served if petitioners are required to pursue endless structural elucidations and quantitations of all metabolites even though some of them might constitute minor fractions of the residue of the sponsored compound. Comments also contended that it may not be experimentally possible to administer to animals sufficient quantities of a compound to obtain amounts of residues sufficient for structural identification. Several comments asserted the studies should be limited to identification of residues in the edible tissues of target animals and that generally it would be unnecessary to have such information on metabolites in inedible tissues. Further, some comments stated that radiotracer studies can be employed to determine the time by which the sponsored compound and its metabolic products are eliminated ("out time"). However, other comments suggested that all metabolites should be identified and tested for toxicity.

The Commissioner reiterates that the objective of requiring metabolic studies is to assure collection of sufficient scientific information on residues to permit a food safety evaluation which in turn can be used to establish parameters for regulatory assays. Therefore, he has concluded that the following metabolic studies are necessary to permit a determination of whether the proposed use of a sponsored compound is safe.

B. Conduct of Metabolic Study

1. *Test animals.* The metabolic fate of an administered compound in an animal may be unique for each livestock production class. Therefore, the Commissioner concludes that a metabolic study in the animals for which a sponsored compound is intended (target animals) is necessary. If the petitioner can demonstrate that the data from the metabolic study obtained for one production class are applicable to a second, the Commissioner may modify the extent of investigation required for the latter.

2. *Required technology.* Because the metabolic fate of a compound administered to food-producing animals plays a pivotal role in decisions regarding the need for an extent of carcinogenesis testing required to assure public health and safety, it is mandatory that such fate be adequately determined, i.e., it must be demonstrated that residues of potential carcinogenic significance have been detected at levels obtainable by the best analytical technology available. Therefore, the Commissioner concludes that the required metabolic studies shall be conducted with the best analytical methods technology can provide.

As will be seen in part VI of this preamble, it is necessary to select one residue that can serve as a practical indicator to assure that the no-residue requirement of the act is met. Such a residue can only be selected by reference to a metabolic study in which residues are detected and measured at levels dictated by the outcome of actual carcinogenicity testing. Because these levels cannot be known at the outset of this phase of the metabolic study in target animals and because the "best available technology" may not be adequate to measure the levels dictated by the outcome of carcinogenicity testing, it may be necessary to develop improved technology and to repeat the metabolic study in target animals, after carcinogenicity testing has been completed. Another requirement of the second metabolic study will be the development of enough data to construct tissue concentration-time profiles for some residues.

3. *Analytical techniques.* For the foreseeable future, the general technique of choice for metabolic studies will be the use of radiotracers. The regulations, therefore, recommend that the required metabolic studies be conducted with radiolabeled compounds of the highest specific activity that is available and is consistent with principles that assure scientific quality. These principles concern the types, the chemical nature, the chemical and metabolic stability, and the suitability of radiolabels for metabolic studies having specific objectives. They have been developed from past metabolic studies with radiotracers and should be followed to assure the scientific quality of the required metabolic studies.

The task of experimental residue detection can often be made easier by available information on the metabolism of related compounds. It is recommended that metabolically feasible pathways applicable to the sponsored compound be proposed based on relevant literature references about compounds of similar structure. This information can usually simplify the choice of radiolabel positions which will assure that all residues containing structural moieties of potential toxicological concern can be detected. However, such projections of likely metabolism can never be a substitute for experimental observation of the metabolic fate of the sponsored compound.

Although the use of radiotracers is the preferred experimental procedure, some compounds possess inherent physicochemical characteristics (e.g., strong fluorescence associated with the structural moiety of potential toxicological significance) that will allow the necessary detection of residues. In such cases, the use of radiolabels may not be required.

4. *Dose regimen.* The dosing regimen for the metabolic study in the target animals shall be consistent with the maximum proposed use level and duration of exposure to the sponsored compound. For compounds administered continuously over long periods of time, administration for the metabolic study need continue only until equilibration or saturation of edible tissues has been demonstrated.

The metabolic fate of a compound administered to target animals is likely to depend on the conditions (level, method, and duration) of use. Because the purpose of the required metabolic studies is to characterize and quantitate residues under conditions of proposed use, these conditions shall be followed in the metabolic studies. However, it is possible that under such conditions certain residues are produced in amounts that do not allow extensive chemical characterization. If the structure of any such residues must be determined, and residues can be produced in sufficient amounts by administering to target animals larger doses of the sponsored compound, the petitioner will be allowed to follow this procedure. In some instances, chemical synthesis of residues may be more feasible, especially if they are needed for chronic toxicity testing.

5. *Required data.* Since the relative persistence of residues in edible tissues is

01151

one consideration in selecting specific residues for toxicity testing, the regulations require that the total number and the relative quantities of residues shall be determined immediately following cessation of treatment, as well as some later time. The Commissioner has concluded that the identification process shall ordinarily continue until the total residue burden in the edible tissues of the target animals has depleted through at least three half-lives. After such time, it is unlikely that new residues previously undetected will appear to alter the residue picture.

The need for and extent of chemical characterization of residues depend on a number of factors. Ordinarily, compounds that constitute a significant fraction of the total residue require sufficient physical and chemical characterization to ascertain whether or not a structural change has taken place which could increase the carcinogenic potency of the residue over that expected of the sponsored compound. In some instances, it may be impossible to judge whether the residue has carcinogenic potential, but significant structural alteration alone may be enough to signal the need for further characterization. Since such structural changes are not uncommon during metabolism and since it is the tissue residues to which human beings will be potentially exposed, such characterization will normally be required. When the agency determines a component of the residue requires chronic toxicity testing (because of tissue concentration and persistence and/or exportation of increased carcinogenic potential), chemical characterization will ordinarily have to be complete and an effort to obtain sufficient quantities of the residue(s) for toxicity testing will be necessary. (See, however, paragraph III.C., below in this preamble.)

In some instances, a petitioner may be required to pursue the complete characterization of certain relatively minor metabolites if partial physiochemical characterization indicates that a structural change during metabolism in the target animal has introduced molecular moieties of carcinogenic potential greater than that expected of the sponsored compound, e.g., nitrosation of an amine of unknown carcinogenic potential to product nitrosamines of known carcinogenic potential.

Because uncharacterized tissue residues pose a risk to public health, the regulation requires that the procedures for separation, purification, and characterization be consistent with the best available scientific and technological capabilities. Ordinarily, the agency will require attempts at characterization to include use of a variety of procedures based on the various forms of chromatography, spectroscopy, and spectrometry.

6. *Format for data submission.* The Commissioner has concluded that the format for presenting results of metabolic studies should be standardized to minimize possibility for misinterpretation of data. Because these studies will provide the basis for major public health decisions, the Commissioner considers it essential that they be carried out and reported in a manner consistent with the best available criteria. The two professional societies listed in the regulations (American Chemical Society and American Society of Biological Chemists) follow policies for acceptance of manuscripts that embody the best available criteria for collecting, interpreting, and reporting scientific data of the type required by this regulation.

C. COMPARATIVE METABOLISM STUDY TO AID IN ASSESSING CARCINOGENICITY OF INTRACTABLE RESIDUES

1. *Sponsored compound always tested: Rationale and procedure.* When it is determined that a sponsored compound has the potential to contaminate edible tissues with residues whose consumption may pose a human risk of carcinogenesis, the sponsored compound itself shall always be tested for carcinogenesis. Residues are selected for testing according to those criteria already discussed in paragraph III.B., but there are overriding reasons for testing the sponsored compound, even if it is not detected as a residue. Metabolic transformation or nonenzymatic degradation of a sponsored compound can lead to a number of tissue residues which cannot be obtained (either by isolation or synthesis) in sufficient amounts for carcinogenicity testing (such residues are herein and in the regulation referred to as "intractable residues"). Testing the sponsored compound itself therefore provides one experimental means for acquiring data on the carcinogenic potential of such residues.

Although the dominant criterion for selecting test animal species or strains for chronic toxicity testing will be the degree to which a species or strain models man, the application of a secondary criterion for selection can provide a means for addressing the problem of intractable residues. Specifically, selection of test animals can also be based on comparative metabolism data (target animal and test animal) which can be used to determine the extent to which particular species or strains, by virtue of the way they metabolically convert the sponsored compound, will be exposed during testing to the same complement of residues expected in tissues derived from target animals.

For example, if a metabolite detected as a residue in edible tissues of the target animal is determined to be toxicologically important, the petitioner will be asked to pursue isolation or synthesis of the compound for toxicity testing purposes. If all attempts at this fail, then the comparative metabolism approach is available if a potential test animal species is shown to produce the same metabolite when it is administered the sponsored compound. In this way, there is some degree of assurance that the toxicity test of the sponsored compound also provides some estimate of the toxicity of the intractable metabolite. Because human food could be contaminated with the intractable metabolite, such a test provides a practical approach to a complex and important issue.

This construct has been included in the final regulations in response to comments that either suggested that all metabolites ought to be ignored (which the Commissioner concludes is neither legally nor scientifically acceptable) or that all metabolites must be isolated and independently tested (which is not technologically possible).

2. *Selection of residues for chronic toxicity testing.* On the basis of all of the studies described above, the Commissioner will select those residues, in addition to the sponsored compound, that require chronic toxicity testing.

IV. CHRONIC TOXICITY TESTING

The sponsored compound and any residues selected for testing shall be subjected to oral, lifetime, dose-response studies in two of the test animal species/strains selected in accordance with the criteria described in the foregoing paragraphs. The purpose of these studies is to determine if the compounds under test are carcinogenic and, if so, to establish the lowest limit of reliable measurement that must be achieved by any regulatory assay for monitoring residues resulting from use of the sponsored compound.

Several comments on this feature of the proposal dealt with the testing of chemical compounds for carcinogenic potential, and addressed two major issues: (i) The design of chronic studies, and (ii) the relevance of animal testing in evaluating human safety.

The Commissioner appreciates the inherent complexity of these issues. He further recognizes that they are common to many areas of food safety, as well as environmental safety, and must be dealt with in an integrated manner in forthcoming regulations on general food safety. However, he believes some discussion of these issues must be included in this preamble as they relate to the context of this regulation.

A. DESIGN OF CARCINOGENICITY STUDIES

Comments on the proposal expressed a variety of contrasting opinions regarding the design features of carcinogenicity studies with experimental animals. The comments specifically addressed: (i) selection of appropriate test animals; (ii) conditions, levels, and duration of exposure; and (iii) statistical design as it relates to number of animals in bioassay, distribution of animals to the various levels of exposure, and adequacy of controls.

The Commissioner recognizes that the impact of these design features on the meaning of animal carcinogenesis data is an important and controversial matter that is currently the subject of intense scientific investigation. The major effort at FDA's National Center for Toxicological Research is specifically directed towards development of relevant protocols and experimental designs for carcinogenicity testing. Until these efforts are concluded and the results incorporated into regulations, the Commissioner recommends that guidance be found in the

01152

report of the Food and Drug Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis, Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides ("Toxicology and Applied Pharmacology," 20:419–438, 1971). This report reviews and analyzes all facets of experimental design that have been developed and scrutinized by competent scientists prior to 1971. To facilitate incorporation of later developments in testing standards as they have and will evolve, the regulations suggest that petitioners submit developed protocols to the Commissioner for review and updating prior to initiating studies.

B. RELEVANCE OF ANIMAL TESTING IN EVALUATING POTENTIAL FOR HUMAN CARCINOGENESIS

Several comments on this aspect of the proposed regulation dealt with the merits of animal testing as an experimental tool. Some comments pointed out that even animal testing done under the best experimental protocols can never prove conclusively that a compound is not carcinogenic, and that under such circumstances, some weak carcinogens are likely to escape identification. Other comments expressed the contrasting view that adequate protocols can be devised. Still others questioned the propriety of drawing conclusions about human carcinogenesis from data collected with experimental animals.

The act requires that in assessing the safety of animal drugs, the carcinogenic potential of residues shall be evaluated. Ordinarily, such evaluation must be based on appropriate testing. Given the gravity of the decisions that depend on the results of such evaluations, the best relevant scientific information must be developed and assembled. As a source of information, direct carcinogenesis testing of chemical compounds in man is and must remain beyond the ethical bounds placed by society on human experimentation. In the absence of this source of information, which incidentally would be most relevant, alternate sources are human epidemiology studies and animal experimentation. Human epidemiology may provide post facto information about the carcinogenic effects of chemical compounds on man. However, while potentially useful in assessing the significance of new exposures or the risk posed by related compounds, such experience cannot be a central basis for food safety evaluations for several reasons, including the same ethical objections that make direct experimentation in man unacceptable.

The Commissioner therefore concludes that the agency must continue to rely on animal testing for the evaluation of the safety for humans of chemical compounds proposed for use in food-producing animals. Moreover, the act does not distinguish between compounds demonstrated to be carcinogenic in test animals and human carcinogens. Instead, it assumes without proof that an animal carcinogen may be carcinogenic in human beings. In this context, the issue of relevance to man of data from tests in animals must be refocused. The regulatory objective must be to avoid falsely negative determinations of the carcinogenic potential of compounds under test in experimental animals that are appropriate models for man. In this setting, the only tenable regulatory posture for the agency is to select bioassay protocols which utilize test-animal species/strains that have the greatest possible susceptibility to the test compound and are also appropriate models for man. Available toxicologic and metabolic information shall provide a basis for such selection.

C. INTERPRETATION OF TEST DATA—IS THE COMPOUND A CARCINOGEN?

The objective of collecting and interpreting test data is to decide whether or not the compound under test (the sponsored compound and any selected metabolites) is a carcinogen. Within certain limits of confidence, statistical treatment of chemical carcinogenesis data can provide objective criteria for such determinations. To the question "Is the tested compound a test-animal carcinogen?" statistics can provide one of two types of answers:

(i) With "x" percent confidence (i.e., in "x" cases out of 100), "y" dose of the test compound will increase the carcinogenesis risk of test-animals over controls by no more than "s" and no less than "t"; or

(ii) With "x" percent confidence, "y" dose of the test compound will increase carcinogenesis risk of test animals over controls by no more than "s."

Answers of the first type are possible only when the observed incidence of carcinogenesis in the test animals is significantly greater than that in the controls. When the observed incidence is the same for test and control animals, only answers of the second type are possible.

A statistically significant increase in the incidence of carcinogenesis in test animals (i.e., an answer of the first type) is sufficient evidence to classify the test compound as a test-animal carcinogen. Because the act does not distinguish between human and animal carcinogens, for the purpose of these regulations, classification of a test compound as a test-animal carcinogen brings into play the requirements of the anticancer clauses. Revisions of such classification on the basis of phyllogenetic considerations can have no bearing on the applicable legal requirements.

If the animal test data will permit only answers of the second type, the decision whether to classify the test compound as a test-animal carcinogen is more difficult. A negative test finding, as pointed out in some comments, can mean either that the test compound is not a test-animal carcinogen at the tested dose, or that the bioassay protocol lacks a sufficient number of animals, or animal susceptibility, or both, to discern an increase in the risk of carcinogenesis in the test animals. In such cases, a decision must be made whether to classify a tested compound as a noncarcinogen or to require further experimentation appropriate for resolving questions of safety.

V. OPERATIONAL DEFINITION OF THE NO-RESIDUE REQUIREMENT

A. ALTERNATE OPERATIONAL DEFINITIONS

If its has been determined that a sponsored compound, when administered to food-producing animals, has the potential to contaminate edible tissue with residues whose consumption may pose a risk of human carcinogenesis, the agency cannot approve the sponsored compound unless it can be demonstrated that conditions of use can be established that ensure the no-residue requirement of the act can be met. To establish such conditions of use and to provide a means for ascertaining whether these conditions are met in actual practice, some operational definition of the term, "no residue," is necessary. Indeed, the act contemplates that the Commissioner will provide such an operational definition, for he must have some criteria for prescribing or approving methods of examination for measuring residues.

The Commissioner has considered three alternate approaches to an operational definition of the phrase. Under one approach the term, "no residue," might be operationally defined as satisfied when the levels of residues fall below those that can be measured by available analytical methodology (alternative 1). A second approach would be to establish some low finite level (e.g., one part per billion) as a "practical zero" and to require assays that can reliably measure this "zero," insisting on the development of new assays if available assays were not adequate (alternative 2). Finally, "no residue" might be operationally defined on the basis of quantitative carcinogenicity testing of residues and the extrapolation of test data using one of a number of available procedures to arrive at levels that are safe in the total diet of test animals and that would, if they occurred, be considered safe in the total diet of man. Under this approach, the Commissioner would require assays that can reliably measure that safe level in edible tissues (alternative 3). For the reasons discussed in section V.B. of this preamble, the Commissioner has concluded that alternative 3 should be adopted. The results of the carcinogenicity testing of the sponsored compound and any selected residues shall be treated by the statistical procedures described in this part V and prescribed in § 500.87 (21 CFR 500.87).

B. CHOICE OF AN OPERATIONAL DEFINITION

1. *Alternative one.* A number of assays might be developed to measure the concentration of a chemical compound (i.e., residue) in an edible tissue, but for each there would be some level below which the compound under analysis could not be measured. (See section I.B. of this preamble). Generally, different assays for the same chemical compound will have different, and sometimes vastly difficult, lowest limits of measurement. The "no residue" requirement of the act could be translated into an operational definition that is based solely on available analytical methodology and specifically on the lowest limit of measurement of an avail-

01153

able assay. Thus, the degree of public risk associated with the use of a sponsored compound would become a function solely of the capability of available analytical technology.

The Commissioner concludes that this approach is unsound because it ignores all quantitative aspects of carcinogenicity testing. The carcinogenic potency of different chemicals varies widely; failure to consider this fact in developing criteria for the evaluation of sponsored compounds would be scientifically unsound. It could produce situations in which residues of extremely potent carcinogens were not measured in edible tissues at levels as low as the measurable levels of residues of relatively weak carcinogens, if the assay available to measure the former happened to have a lowest limit of measurement that was higher than that of the assay available to measure the latter. Accordingly, failure to consider quantitative carcinogenicity data in establishing the criterion of lowest limit of measurement that an assay must meet would be tantamount to ignoring public health protection in evaluating the use of sponsored compounds.

2. *Alternative two.* A second approach the Commissioner has considered would be to establish "practical zero" for the residues of all carcinogens. This approach would have one advantage over alternative one; it would provide a well-defined criterion for the lowest limit of measurement that any petitioner's assay would have to satisfy. This approach would not, however, take into account differences in carcinogenic potency among various carcinogens and is therefore unacceptable for the same reason as alternative one.

Under alternative two the criterion for lowest limit of measurement would reflect consideration of what lowest level of measurement is "practical," given the state of the art of analytical chemistry or biochemistry. In addition to failing to link the no-residue standard to any consideration of carcinogenic potency, this approach fails on the ground of practicality. The science and technology of analytical chemistry and biochemistry are continuously changing, and a lowest limit of measurement which might be considered reasonable at one time would have to be discarded as unreasonable at some later time. Whenever a new and lower criterion for the limit of measurement were established, it would be incumbent upon the Commissioner to then require that use of all compounds approved under the prior criterion be suspended until methods were developed to measure the residues at this lower level. Such a situation, in the Commissioner's judgment, would be both unreasonable and unmanageable.

3. *Alternative three.* A third approach to defining operationally the no-residue requirement is to establish a required lowest limit of measurement for each sponsored compound on the basis of data derived from carcinogenicity testing of the compound and selected metabolites. Under this approach carcinogenic potency is given specific consideration because actual chronic toxicity test data are used to determine the level of residues in edible tissue that an assay must be capable of reliably measuring. Thus, it permits a rational, uniform procedure for establishing the required lowest limit of measurement for assays and avoids the major deficiencies inherent in alternatives one and two.

Should new information relating to the carcinogenic potency of residues of a sponsored compound later appear, this approach provides a practical basis for determining whether a new assay is required to establish compliance with the no-residue requirement. But only under such circumstances will it be necessary for the Commissioner to insist that the petitioner develop a new assay; thus, this approach contributes to regulatory stability and predictability. If an assay becomes available with a lowest limit of measurement that is lower than the level required by the analysis of quantitative carcinogenicity data, the Commissioner will adopt that method if it also meets the other rigorous criteria described in part VIII of this preamble and § 500.90 (21 CFR 500.90). However, for compounds that have been approved for use on the basis of an assay that satisfies the requirements of the regulation, the development of such a method will not be required. Thus, following this approach, the Commissioner can provide the maximum public-health protection based on both quantitative carcinogenesis data and improved analytical technology. For these reasons, the Commissioner concludes that alternative three is the most rational approach to developing an operational definition of "no residue."

By adopting this approach to implementing the "no residue" standard, the Commissioner has assumed that: (i) The carcinogenic potency of chemical compounds can be quantified, and (ii) a dietary level of a carcinogen can be identified at which no significant human risk of carcinogenesis would derive from consumption of food containing residues below this level.

The carcinogenic potency of compounds can be determined by testing in experimental animals, although such determinations are subject to known limitations inherent in every measuring device or system. The second assumption, that potential residue levels representing no significant human risk of carcinogenesis can be assigned, is controversial, but it must be fully confronted and resolved if the public is to be protected from the potential and real dangers that inhere in the interpretations of the no-residue standard of the act outlined as alternatives one and two.

C. ANALYSIS OF ANIMAL CARCINOGENESIS DATA TO DEFINE OPERATIONALLY THE NO-RESIDUE STANDARD OF THE ACT

1. *Introduction.* The modified extrapolation procedure of Mantel and Bryan proposed for use in defining the no-residue standard for a sponsored compound is a statistical technique that allows estimation of the level, or dose, or a carcinogen that would lead to cancer incidence rates in test animals well below those rates that can be detected in practical experimentation. In normal experiments in which test animals are administered various levels (doses) of a suspected carcinogen, the observed responses (i.e., the percent of test animals developing cancer if the compound is carcinogenic) are usually in the range of about 5 percent to 95 percent. To observe responses at incidence rates less than about five percent requires large numbers of test animals. As will be seen, experiments designed to observe responses in the range of interest in establishing the no-residue standard, would require very large and often impractical populations of test animals. Therefore, the procedure of Mantel and Bryan,[1] and Mantel et al.,[2] as modified, is used to treat statistically the dose-response data from actual experimentation and to estimate the dose or level of the compound under test that would result in lifetime test-animal cancer rates no higher than a certain preselected rate.

Before discussing the many comments received on this feature of the proposal, the Commissioner reemphasizes that some operational zero must be defined if the no-residue requirement of the act is to be implemented. Regardless of the arguments for or against the Mantel-Bryan procedure, the Commissioner maintains that a procedure that takes into account the carcinogenic potency in test animals of residues (which the Mantel-Bryan procedures does) is far superior to any approach that fails to do so.

The modified Mantel-Bryan procedure described in the proposal was labeled excessively conservative by some comments and recklessly liberal by others. Those who considered the procedure too conservative objected to the proposed use of a series of conservative assumptions (shallow-slope, dose-response relations, low acceptable level of risk) and contended that any one of these assumptions alone could provide adequate protection to the public. Further, these comments argued that the practical application of the procedure has not been demonstrated, and suggested that it would prohibit the use of many valuable compounds. Persons who considered the proposed procedure too liberal objected to the proposed use of a lower confidence limit on the observed slope of the dose-response curve. Their objection is that the proposed statistical technique for extrapolating dose-response data obtained from animal tests seriously underestimates public risk. The technique provides a basis for establishing a dose level where there would be no significant human risk of cancer, thereby establishing a criterion for a residue detection method. Specifically, the comments contended that if the true statistics of the dose-response relation are logistic or linear, ex-

[1] Mantel, N. and W. R. Bryan, "'Safety' Testing of Carcinogenic Agents," "Journal of the National Cancer Institute," 27(2):455-470 (1961).

[2] Mantel, N., et al., "Improved Mantel-Bryan Procedure for 'Safety' Testing of Carcinogens," "Cancer Research," 35:865-872 (1975).

trapolation with the slope of a probit transformation would seriously underestimate public risk. Further, these comments argued that the probit transformation leads to a paradox, in that strong carcinogens are treated less conservatively than weak ones. Regardless of their point of view, however, most of the comments supported the Commissioner's effort to elicit public discussion of the implementation of the anticancer provisions of the act.

2. *Choice of the Mantel-Bryan procedure*—(a) *Alternative statistical models.* Most of the comments favored the proposed adoption of the Mantel-Bryan procedure but without the modifications suggested in the proposal. A smaller number of comments recommended that a linear extrapolation would be a better alternative to the Mantel-Bryan procedure, and even fewer suggested the logistic or the angle distributions. Still other comments suggested that a comparative analysis of animal carcinogenesis data be required employing all alternative distributions and the smallest estimate of the "safe" level be used to define the no-residue standard for a compound. Finally, some comments indicated that, although the logistic and angle distributions have been used in biological sciences, there is no indication that either one provides advantages over the probit (Mantel-Bryan) or the linear distribution, and that, therefore, neither was appropriate for regulatory purposes.

Some comments favoring the Mantel-Bryan procedure argued that it has a theoretical rationale which is probably relevant to the carcinogenic action of chemical agents. A similar argument was made by some of the comments favoring the linear extrapolation. These comments also contended that the linear extrapolation has the public health advantage of being the most conservative of all procedures.

(b) *Limitations in available procedures and choice of procedure.* The Commissioner has extensively reviewed the known procedures that may be used to derive an operational definition of the no-residue standard of the act from animal carcinogenesis data. This review has persuaded him the same scientific and technological limitations are common to all. Specifically, because the mechanism of chemical carcinogenesis is not understood, none of these procedures has a fully adequate biological rationale. All require extrapolation of risk-level relations from responses in the observable range to that area of the dose-response curve where the responses are not observable. Matters are further complicated by the fact that the risk-level relations adopted by the various procedures are practically indistinguishable in the observable range of risk (5 percent to 95 percent incidence) but diverge substantially in their projections of risks in the unobservable range. Finally, the Commissioner concludes, no procedure is intrinsically more conservative than any other; the conservatism of any procedure depends entirely upon the restrictions and modifications imposed.

The comments failed to demonstrate that another procedure is superior to that of Mantel and Bryan [1] and Mantel et al.,[2] (Mantel-Bryan) and therefore the Commissioner has adopted it with some modifications. Moreover, the Commissioner concludes that some aspects of the Mantel-Bryan procedure offer distinct advantages over the other statistical procedures. It provides a clearly defined means for pooling data from multiple experiments and from multiple dose levels within a single experiment, thus permitting decisions based on the fullest use of available data. Further, the Mantel-Bryan procedure has a clearly defined mechanism for handling the spontaneous tumor rate. (See paragraph V.C.4.(d) of this preamble, below.) To overcome certain limitations of the Mantel-Bryan procedure, the Commissioner has adopted a number of modifications, which are described in § 500.87 and discussed in paragraph V.C.4 below in the preamble.

The Commissioner recognizes the significance of the decision to adopt the modified Mantel-Bryan procedure to implement the no-residue requirement at a time when that procedure, and similar procedures, as well as the relationship between test-animal experience and human risk, are under active and intense scientific study. He therefore has concluded that a review of this decision shall be undertaken in 2 years, and any appropriate modifications in the regulation will then be initiated.

3. *Time-to-tumor and other considerations.* Several comments contended that the proposal was deficient because it did not address the time-to-tumor aspects of chemical carcinogenesis. Some comments pointed out that Albert and Altshuler have developed preliminary statistical relationships between low levels of carcinogen exposure and time of tumor manifestation. It is the view of these authors that characterization of carcinogenic potential on the basis of incidence alone is not appropriate, because it ignores the life-shortening aspects of carcinogenesis.

The Commissioner generally agrees with these comments. He is faced, however, with a dilemma similar to that presented by the choice of statistical distributions. While statistical analyses based on incidence have been subjected to the scrutiny of use, the time-to-tumor relations developed by Albert and Altshuler have not. For this reason, the Commissioner concludes that the basis for extrapolation prescribed in the regulation shall be only incidence statistics, but the agency will initiate a review of the matter of time-to-tumor statistics in 2 years and consider the desirability and practicability of providing for their consideration.

One comment stated that "effects produced at higher dose levels * * * are useful for delineating the mechanism of action, but for any material and adverse effect, some dose level exists for man or animal below which adverse effects will not appear." The comment analyzed in detail the deficiencies of all statistical extrapolations and stated that approaches are available to define a true carcinogenic "no-effect" level. It contended that it is more appropriate to determine a biologically insignificant level using a safety factor based on competent scientific judgment.

The Commissioner disagrees with the contention that the classical toxicology concepts of "thresholds" and "biologically insignificant levels" are generally applicable to carcinogenesis. There is substantial scientific controversy over whether such concepts apply to irreversible processes, such as the chemical induction of malignant neoplasia. "Threshold" and "biologically significant level" concepts derive from short-term toxicity experiments which have no established meaning in biological processes that require long latent periods (up to 20 or 30 years) before lesion manifestation.

Several comments opposing the proposal suggested that the agency should maintain flexibility and evaluate the approvability of sponsored compounds based on assessments of benefit and risk, in effect offering another approach to establishing the operational zero for carcinogenic residues. The Commissioner concludes, however, that an approach that contemplates consideration of the benefits of use of a sponsored compound in defining the no-residue standard is incompatible with the anticancer provisions of the act.

4. *Modifications and restrictions on the Mantel-Bryan procedure*—(a) *Expression of dose level.* Several comments addressed the adjustments the Commissioner proposed to make in the "safe" level of Mantel and Bryan derived from the experimental animal data in order to establish an appropriate value for man. Some comments stated that adjustments for differences in food intake between experimental animals and man inappropriate when dealing with carcinogens. The comments stated that such adjustments would assume erroneously that all toxic materials have the same mode of action on a body weight basis. They further suggested that the relationship should be expressed in terms of concentration in the feed of the test animals and in the food of man when the diet in both cases is consumed ad libitum, other than on an amount-per-body-weight basis. Other comments argued that the conversion of animal data to man should be based on surface areas.

The final regulations specify that carcinogenicity tests shall be conducted with the test compound's concentration in the diet of the experimental animals held constant throughout the study. And the "safe" level derived from the modified Mantel-Bryan extrapolation of test-animal data shall be expressed as a concentration in the total diet (weight of compound/weight of total diet) of the animals and shall be directly applied at the "safe" level for the total diet of man. The Commissioner concludes that the arguments for conversion based on surface areas or on intake per unit of body weight have little basis. The comments

01155

provided no evidence that these concepts are applicable to low-dose chronic exposures. The surface area concept is based on experience with short-term, high-dose studies. Furthermore, measurements of surface area are crude. Finally, surface area and body weight will vary, as will food intake per day, throughout the chronic study, thus requiring constant adjustments of dose.

Until evidence is compiled demonstrating that there is a more appropriate means of conversion from experimental animal to man with respect to chronic exposure and carcinogenic manifestation, the Commissioner will assume that the animal is the integrator throughout its lifetime of any observed response to a fixed concentration in the diet. The Commissioner has thus adopted the direct conversion approach (the "safe" level in parts per million, parts per billion, etc., of the diet of the experimental animals directly applied to the diet of man), which is the most conservative, as well as most practical, of the approaches considered.

(b) *Degree of data confidence.* The Commissioner disagrees with comments that characterized the proposal's requirement for 99 percent confidence intervals as another in a series of unnecessarily conservative assumptions. Confidence intervals characterize the quality of experimental measurement. The Commissioner concludes that a high degree of confidence should be demanded for decisions respecting carcinogens. He therefore has adopted the 99 percent level of confidence, and the final regulations require that all calculations based on experimental observations shall be made from or with the 99 percent confidence limits.

(c) *Slope used for extrapolation.* The proposal would have required that extrapolation be made with the lower 90th percentile of the observed dose-response curves. Numerous comments stated that the extrapolation should be performed with a slope of one, as proposed by Mantel and Bryan.

The Commissioner agrees with comments that suggested that use for extrapolation of the observed slope of the experimental dose-response curve could underestimate public risk, and has modified the regulation to call for a maximum slope of one. This requirement affords a high degree of confidence that, regardless of the actual configuration of the dose-response curve in the unobservable region, the maximum projected risk will be higher than the actual risk.

If the experimental dose-response curve exhibits a slope that is less than one, it is possible that this slope characteristic may also prevail in the unobservable region. To maintain the conservatism of the procedure, in such situations, the regulations require that the extrapolation be performed with the shallower slope. The Commissioner recognizes that there may be weak carcinogens whose actual dose-response curve slope may be relatively steep at the lower levels of response, with a plateauing (i.e., very shallow slope) in the experimentally observed region. In such a case, the procedure adopted would be ultraconservative. However, it is not possible to know the nature of the true slope in the unobservable region, and the agency must have a high degree of confidence that the maximum projected risk is above the actual risk.

(d) *Spontaneous tumor rates and data combination.* In the proposal the Commissioner recognized certain limiting features that are common to all extrapolation procedures, including that of Mantel and Bryan. These limitations concern the rate of tumor incidence in the control groups of animal bioassays and the selection or combination of data from different experiments. Since publication of the proposal, Mantel and coworkers[2] have developed procedures to deal with these issues. The Commissioner sees merit in these improvements and has adopted them in the final regulations.

In the original procedure published by Mantel and Bryan, the tumor incidence attributable to a given level of a chemical carcinogen was measured as the difference between the upper 99 percent confidence limit of the observed response of test animals and the lower 99 percent confidence limit of the observed response of control animals. The effect of this procedure on the derived "safe" level is minor when the tumor rate in control animals is low; however, when the control animals exhibit a high rate of spontaneous tumors, the effect of the procedure is far more pronounced. The improved procedure published by Mantel et al.[2] treats the rate of spontaneous tumors as an additional statistical parameter, which it is, and thus resolves this problem.

In many instances, the male and female animals of the same strain may exhibit significantly different responses to a compound. It is also apparent that the responses of different strains and species may be similar. It is always desirable to make maximum use of available information by appropriate combination of different data sets however, but prudence must govern the process of selecting and combining data. Combining different data sets increases the number of animals used in the analysis and therefore increases the confidence in the results. Yet, in many instances, different data sets contain different types of information. Mantel et al.[2] discuss the informational aspects of data combination with respect to pooling data from different experiments and from different doses. The Commissioner agrees in principle with most of their conclusions; nevertheless, he anticipates that situations will arise where the evidence in support of combining or not combining data will be equivocal. Therefore, he concludes that the statistical and biological evaluation of data will determine which data sets, if any, will be appropriate for pooling. Where there are significant statistical and/or biological differences in the observed responses, only subsets of data representing statistically and biologically compatible bioassays will be used for analysis.

(e) *Level of risk.* The proposal suggested that an accepted level of risk for test animals, and thus for man, could be 1 in 100 million. Many comments argued that this level of risk was unnecessarily conservative in light of the many other cumulative, conservative restrictions already imposed by the regulations. For the reasons set forth below, the Commissioner has concluded that this level of risk is unduly limiting without substantial compensation in terms of public health.

As the level of risk is decreased, the number of animals that are required in each test to bring the lowest limit of the assay's measurement derived from a no-carcinogenic-response test into the range of current analytical technology vastly increases. Thus, the time and resources that are necessary to plan, perform, and evaluate the test before submission to the agency in proper form increase enormously. This in turn increases the potential for interference from irrelevant variables or intervening forces. Then the amount of agency resources that must be committed to evaluate the data also increases almost geometrically. Finally, all these additional factors provide only a minor incremental increase in the degree of confidence in any decision that must be made on the results of these chronic toxicity tests. Consequently, the final regulations establish the maximum risk to be used in the Mantel-Bryan calculation as 1 in 1 million. The following clarifications of the meaning of the 1 in 1 million risk level demonstrate why the Commissioner believes that such a risk level can properly be considered of insignificant public health concern.

(i) The risk level of 1 in 1 million is a risk level for the entire lifetime of an individual.

(ii) This lifetime risk is the maximum, and therefore unlikely, human risk level. Because of the series of conservative assumptions built into the modified Mantel-Bryan procedure and into the derivation of the final "safe" level (see paragraph V.D., below in this preamble), the most likely human risk level will be several orders of magnitude less than this maximum.

(iii) The 1 in 1 million lifetime risk level assumes that an individual will consume maximum residue levels every day over a lifetime.

(iv) The use of this procedure for estimating acceptable level is based on the assumption that the only risk to the human population is that from residues of the sponsored compound, not from such intervening causes as disease or accidents (e.g., the average risk of fatality by motor vehicle accident per year is approximately 1 in 4,000). Because the population is constantly at risk from a wide range of factors, however, any increment of increased risk associated with exposure to residues of multiple compounds is at most in the vanishingly small range.

01156

D. DERIVATION OF THE LEVEL OF TOTAL RESIDUES OF CARCINOGENIC CONCERN WHICH CAN BE TAKEN AS SATISFYING THE NO-RESIDUE REQUIREMENT OF THE ACT

As explained in the previous section, a potential residue level corresponding to a risk of 1 in 1 million in test animals (i.e., the "safe" level derived from the modified Mantel-Bryan procedure) can be considered the level that represents no significant carcinogenic burden in the total diet of man. This level is assigned in the final regulations the symbol S_0, and, expressed as a fraction in the total diet (i.e., parts per billion, parts per trillion) of the test animals, shall be directly taken as the potential undetected residue level that is safe in the total diet of man.

In some cases, residues in addition to the sponsored compound itself will have been selected for carcinogenicity testing. In these instances, "safe" levels will be derived for each of the compounds that have undergone testing. The compound exhibiting the lowest value for the "safe" level is the most potent carcinogen of those tested and constitutes the greatest potential carcinogenic threat among the residues. The Commissioner will, accordingly, choose the smallest value of the various "safe" levels, assign to it the symbol S_0, and assume that it represents the potential carcinogenic burden that may result from the administration of a sponsored compound to food-producing animals. Additionally, because other tested residues may have exhibited carcinogenic properties (albeit less potent) and still other, untested residues may represent carcinogenic risks, the S_0 will be taken as the sum of the levels of all of the residues. Potential residues in the total human diet cannot exceed S_0 if that diet is to bear no significant carcinogenic risk to man. The only residues that can be excluded from the sum of residue levels are those that have been unambiguously shown to be noncarcinogenic.

Although it will already be apparent to the attentive reader and to the trained scientist, it bears reiteration at this point that S_0 (or any figure derived on the basis of adjustments described below) does not represent a level of residues "approved" for introduction into the human diet. The purpose of these regulations is to establish criteria for the evaluation of assays for the measurement of carcinogenic animal drugs. These criteria must include some lowest level of reliable measurement that an assay is required to meet. In defining a level of potential residues that can be considered "safe," therefore, the Commissioner is establishing a criterion of assay measurement that, if it can be met for a compound, will assure that any undetected residues resulting from the compound's use will not increase the risk of human cancer.

E. CORRECTIONS FOR FOOD INTAKE

Several comments argued for and others opposed further adjustments based on patterns of food consumption. Some comments contended that the "safe" level of Mantel and Bryan in the animal diet should be directly applied as the upper allowable limit in man's diet and in any component food in the human diet. These comments argued that this limit should not be raised by consideration of intermittency of consumption of particular foods or of the proportion of the total diet represented by an individual food. They suggested that individuals who consume above average amounts of food would be exposed to above average, and thus possibly harmful, levels of residues. Further, these comments contended that the act does not provide a distinction between people who consume average diets and people who consume above-average quantities of exotic foods; both groups are entitled to equal protection. They argued that adjustments for exposure frequency based on food consumption patterns assume that continuous long-term exposure to a carcinogen precedes the development of cancer.

Many other comments urged that adjustments should be made based on the proportion of the specific food in the total diet and the frequency of exposure. These comments generally favored the use of food consumption data, so that the degree of conservatism was more uniformly applied taking into account the relationship of the particular food to the total diet.

The Commissioner disagrees with the contention that no adjustments should be made for factors of exposure. Section 512(d)(2)(A) of the act requires the Commissioner to consider the probable consumption of a drug and of any substance formed in or on food because of its use. Analysis of carcinogenesis data provides S_0. The no-residue standards of the act has been defined as satisfied when the sum of the levels of all potential undetected residues of the sponsored compound (excluding only those that have been found to be noncarcinogenic) would not exceed S_0 in the total diet of man. Because products derived from food-producing animals do not constitute the total human diet, it is therefore appropriate that S_0 be corrected for probable human consumption of specific tisues. The Commissioner agrees, however, that any adjustments must be conservative to assure that all segments of the population are protected.

The Commissioner has consulted available data on food consumption patterns in the United States, and concludes that muscle tissue and eggs can be considered, conservatively, to each constitute one-third of the total daily human diet. Since milk can constitute the total daily diet of any individuals (e.g., infants), no adjustment will be made for this commodity. Adjustments for frequency of exposure for tissues other than muscle, milk, or eggs (i.e., kidney, liver, etc.) will be considered only if the proportionate levels of potential undetected residues in such other tissues, compared to muscle, are such that intake of muscle tissue on days when other tissues are not being consumed provides an insignificant contribution to the total exposure to residues (i.e., S_0 is never exceeded in the total diet of human beings).

The final regulations use the symbol S_m to represent the level of total residues of carcinogenic concern that can be operationally defined as satisfying the no-residue requirement of the act for specific tissues. If, for example, a particular animal drug used in cattle were found to have an S_0 of 10 parts per trillion, the assay required for approval of the drug would have to be capable of reliably measuring residues of 30 parts per trillion and above in muscle tissue.

F. OTHER POSSIBLE ADJUSTMENTS

Several comments urged that the regulation should not provide for adjustments for the degradation of residues in food under normal conditions of storage and cooking. Others suggested that such data should not be required but should be taken into account when available. Still other comments expressed the fear that such data would be used to dilute the conservative intent of the regulation; they argued that the term "normal condition of storage and cooking" would be difficult to define, and it might reduce protection in situations where actual storage and food preparation practices did not approximate experimental conditions. Finally, some comments suggested, generally, that such studies should be required only when there is reason to believe that such information would assist in protecting public health.

The Commissioner agrees that the parameters appropriate to such studies have not been defined, and he has deleted from the final regulations references to postslaughter residue degradation studies. When there is reason to believe that storage conditions or food preparation methods might lead to the formation of potentially toxic residue products, however, the Commissioner will require appropriate special investigations. Petitioners are encouraged to explore the postslaughter stability of residues. Experience has shown that residue stability can be a complicating factor in studies for the validation of assays for dosed tissues. The Commissioner encourages research in this area but until appropriate information can be reliably incorporated in the food safety decisions, such data will not be used to liberalize the requirements of the regulations.

G. CONSIDERATION OF OTHER RELEVANT SAFETY FACTORS

Originally, the Commissioner proposed that the Mantel-Bryan calculation be modified to account conservatively for drug use patterns, e.g., the administration of a drug in the treatment of diseased animals. Comments demonstrated that disease incidence does not occur randomly within a geographic area or within specific animal groups. Although a disease may have an overall incidence of only 10 percent, the affected group may be located in a single area. Therefore, the Commissioner is unable to conclude that evidence exists, or other safety factors are available, to permit him to calculate the effect of such drug usage, and he has deleted this provision from the regulation.

01157

VI. Metabolic Study to Select Marker Residue and Target Tissue

A. The Concept

Before he can approve the use of a sponsored compound, the Commissioner must assure that a practical and reliable assay is available that can measure carcinogenic residues at the level which discriminates safe from unsafe food, i.e., the assay must be capable of determining when S_m is exceeded in each edice tissue. One approach to this problem would be to require assays that can be used to measure every residue in each of the various edible tissues. Because the number of residues in edible tissues and the number of tissues can sometimes be large, it is unlikely that such an approach could be put to practical use. The Commissioner has determined that another approach is possible that is far more practicable and sacrifices no principle of safety. This alternative approach centers on the concepts of a marker residue and a target tissue.

A marker residue is a residue whose level in a particular tissue is in a known relationship to the level of the total residue of carcinogenic concern in all edible tissues and which, therefore, can be taken as measure of the total residue of interest in the target animal. Once a marker residue is selected and its quantitative relationship to the total residue is determined, it is possible to calculate a level, for purposes of these regulations, R_m, which is that level of the marker residue that must not be exceeded in a selected tissue (the target tissue) if the total residue of carcinogenic concern in the edible tissues of the target animal is not to exceed S_m. The marker residue can be the sponsored compound or any of its metabolites, or a combination of residues for which a common assay can be developed.

The target tissue is that tissue in which the absence of the marker residue at R_m or above can be taken as confirmation that the safe residue level, S_m, is not exceeded in any of the edible tissues. When a marker residue and a target tissue are selected, a practicable assay must be developed that can reliably measure the marker residue in the target tissue at levels at least as low as R_m, and conditions of use of the sponsored compound must be established that assure that, in practice, the potential marker residue level in the target tissue does not exceed R_m.

When it is determined, using as assay demonstrated to be capable of reliably measuring the marker residue in the target tissue at levels at least as low as R_m, that there is no such residue at levels at or above R_m, it can be concluded that the no-residue standard of the act has been satisfied for all edible tissues in the animal under examination. Conversely, if the market residue is found in target tissue at levels equal to or greater than R_m, all edible tissues must be considered unsafe for human consumption.

B. Application: Data Development and Calculation of R_m

1. *Marker residue.* Application of the concepts of marker residue and target residue requires an experimental determination of the quantitative relationships of residues that might serve as markers (including any which have definitely been shown to be noncarcinogenic, since theoretically one of these might be selected as marker residue) to the total residue in each of the various edible tissues which might serve as target tissues. Further, because these relationships change with time, the levels of potential marker residues in the potential target tissues must be measured over time, and tissue concentration-time profiles must be constructed. These depletion profiles will be derived from measurements made in target animal tissues after cessation of exposure to the sponsored compound. Finally, because the results of carcinogenicity testing have been used to set limits for total potential undetected residues in each of the individual edible tissues, the depletion profiles must include measurements of the total residue in each potential target tissue to levels at least as low as the S_m appropriate to the tissue. Additionally, depletion profiles for one or more potential marker residues must be constructed and include measurements of levels of residues corresponding to the times when the total residue has reached S_m (Plates I and II set forth in § 500.89 (31 CFR 500.89).)

Part III of this preamble describes the requirements for the study of the metabolic fate of a sponsored compound in target animals. Although the purpose of this earlier metabolic study is to provide information for selecting residues for carcinogenicity testing, the same principles and requirements are applicable here and must be followed in acquiring the information necessary to construct depletion profiles. However, to meet the depletion profile requirements prescribed by the regulations, a second metabolic study of the sponsored compound in the target animals may be necessary. This second and possibly more refined study may require the use of a larger number of animals, for it will be necessary to determine the total number and the quantities of residues, not only at two points in time, but at several appropriately spaced time intervals starting immediately after cessation of exposure and continuing until the residues in each of the potential target tissues has reached a level corresponding to a total residue level of the appropriate S_m (e.g., for meat, milk, or eggs). If the initial metabolic study were done with the degree of precision required to select a marker residue and a target tissue, of course, it need not be repeated.

Selection of a marker residue will be based on examination of depletion profiles. Generally, there will be some time at which the sum of the levels of the individual residues of carcinogenic concern will fall below the S_m appropriate to the tissue under examination. Residues that are potential markers will be present at a known concentration (R_m) at this same time (T_L of Plate I), and in a definite (although perhaps rapidly changing) quantitative relationship to the total residue (Plate II).

With the quantitative relationships established, it will be possible to select one of the residues as a marker. Ordinarily, the residue selected will have the following characteristics: (i) It will represent at least 10 percent, and usually a great deal more, of the total residue burden at the time when the total residue was depleted to S_m; (ii) it will be stable, easily isolated and characterized, and susceptible to manipulation for assay development and implementation; (iii) it will be undergoing relatively rapid change in concentration at the time the total residue burden is at or near S_m (i.e., a change in its concentration will be a sensitive indicator of the time when the total residue burden has depleted below S_m. While other considerations may enter into the selection of a marker residue, these three will ordinarily be most important.

There may be instances in which no single residue can adequately fulfill the requirements which a marker residue must meet. In such instances, it may be necessary to select some combination of residues which, taken together, can represent the total residue burden. It should be noted that a marker residue can be a compound which is not a carcinogen, but is an unambiguous indicator, in the manner already described, of the presence or absence of carcinogenic residues.

2. *Target tissue.* Selection of a target tissue requires a comparison of the depletion profiles for each of the edible tissues (Plate I set forth in § 500.89). A target tissue will be selected based on assurance that the absence of the marker residue at or above R_m assures that carcinogenic residues are absent from the slowest depleting tissue, and thus that the entire animal is free of carcinogenic residues:

When a compound is to be used in milk- and egg-producing animals, milk and eggs will be target tissues in addition to one tissue selected as the target tissue to represent the depletion of residues in all of the edible carcass. In such cases, it may be necessary to select a marker residue for milk or eggs that is different from the marker residue selected for the target tissue representing the edible carcass.

3. *Calculation of R_m.* The level of the marker residue which is present in the target tissue at the time (T_L) when the sum of the levels of the residues in the slowest depleting tissue (excluding any residues that have definitely been shown to be noncarcinogenic) is equal to S_m for that tissue, is the R_m for that marker residue. The depletion profiles will be used to select R_m (Plate II set forth in § 500.89).

For example, assume (i) that liver is the target tissue of animal drug, P, intended for use in cattle; (ii) that the

01158

only residues of P are the parent compound, P, and a metabolite P_1; (iii) that T_L is 3; (iv) that S_m for the sponsored compound is 29 parts per trillion; and (v) that the following is a chart of the depletion profile of the drug.

[In parts per trillion]

Time	Total residue burden	P	P_1
0	100.0	75.0	25.0
1	65.4	44.6	21.8
2	42.0	25.3	17.3
3	29.0	15.0	14.0
4	21.0	9.0	12.0
5	15.0	5.0	10.0

In this case, before the drug can be approved for use, the petitioner must develop an assay that will satisfy the evaluation criteria in liver for either P at least as low as 15 parts per trillion or P_1 at least as low as 14 parts per trillion. Because P is depleting faster than P_1, when the total residue burden is 29 parts per trillion, P may be the preferred compound to select as the marker residue since it does provide a more accurate assessment of when the total residue burden reaches 29 parts per trillion (S_m). Another example is provided in Plate II in § 500.89.

VIII. Sponsored Compounds Affecting Pools of Carcinogenic or Potentially Carcinogenic Substances Endogenous to Target Animals

A. Applicability of No-Residue Requirement

The act requires that in making food safety decisions, the Commissioner take into account all substances formed in or on food by the administration of sponsored compounds to food-producing animals. It is well recognized that: (i) Several substances endogenous to food-producing animals are suspect or proven carcinogens; (ii) in any given animal species or breed, the size of pools of such endogenous substances vary widely with such attributes as sex, age, lactation, state of estrus, pregnancy, geographic location, and animal husbandry practices; and (iii) man has had sustained exposure to such endogenous substances for centuries. Whether normal levels of human exposure to these substances are responsible for human carcinogenesis is unknown, but the Commissioner maintains that the use of drugs that can cause an increase in human exposure to such compounds has the potential of increasing the risk of human carcinogenesis. The use of such drugs must therefore be controlled.

In dealing with potentially carcinogenic endogenous compounds, the proposal declared that the intent of the no-residue requirement of the act is the maintenance of the normal human dietary content. Thus, the regulations require the determination of the effects of sponsored compounds on the normal background levels of potentially carcinogenic endogenous compounds. If a compound is found to increase such levels, conditions of use must be established so that normal background levels are not exceeded in the animal when the animal is slaughtered. The regulations also require the development of practical assays for measuring endogenous compound levels.

Several comments on this segment of the proposal expressed concern over the meaning of the term "endogenous compounds" and questioned how such compounds are to be distinguished from "exogenous compounds." Others questioned whether the former term includes chemical derivatives (estradiol benzoate) of bona fide endogenous compounds (estradiol) or essential nutrients (some amino acids, minerals, vitamins). Comments also expressed doubt about the distinction between endogenous and exogenous compounds in cases where the administered compound can be metabolized to residues of both classes. Some comments also argued that all externally administered compounds should be considered exogenous, as the true meaning of the term implies.

Other comments suggested that endogenous substances of interest be subjected to toxicological testing and tolerances be set if such substances are found to be not carcinogenic. Some expressed doubt that available technology could meet the requirements of the proposed regulation. They contended that the terms "normal conditions of use" and "normal background levels of endogenous compounds" would be either extremely difficult or impossible to define. The Commissioner recognizes the difficulty of the task, but concludes that administered compounds that increase the naturally occurring level of potentially carcinogenic endogenous compounds present special problems of control which the regulation must address and resolve.

B. Definitions

An endogenous compound is any compound that is metabolically produced by and is present in untreated target animals. Any sponsored compound that is found to increase the normal background levels of a potentially carcinogenic endogenous compound shall be subject to these regulations regardless of how the increase is brought about.

For instance, estradiol benzoate, which is by the above definition clearly not an endogenous compound, is metabolically converted to the endogenous compound, estradiol, and may thus cause an increase in normal background levels of that substance. Estradiol may itself be administered, possibly again causing target animal pools of estradiol to increase above background. Finally, a sponsored compound may indirectly cause an increase in tissue levels of estradiol by affecting any number of hormonal regulatory systems in the target animals. While in each of the above cases the cause of the increases in normal background levels of estradiol was different, the result was the same. And it is the result that must be monitored and controlled. It is thus of little use to distinguish between "endogenous" and "exogenous" sponsored compounds. Rather, it is useful only to distinguish between administered compounds that can cause changes in normal background levels of potentially carcinogenic endogenous compounds, which can unambiguously be defined, and those administered compounds that do not affect such levels.

Essential nutrients are not included in the definition of the classes of compounds that will be regulated by these regulations. In a strict sense, essential nutrients are not endogenous. Although present in the tissues of animals and required for growth and health, they are not produced by the animals and must be supplied from external sources. These features place essential nutrients in a distinct class of "required exogenous compounds," which must continue to be regulated in a unique manner. Determination of the allowable use of essential nutrients must reflect the nutritional requirements of the target animals. When used according to label directions, essential nutrient supplements should restore but must not exceed the essential nutrient levels found in natural foods adequately sustaining normal growth of healthy animals. Furthermore, the levels of animal essential nutrients found in human food derived from supplemented animals must not exceed the levels in food derived from normal healthy animals fed a nutritionally adequate natural diet.

C. General Procedures

If available information shows a sponsored compound might affect pools of potentially carcinogenic endogenous substances in target animals, and cause an increase in the level of such substances above the level considered to be safe by the criteria of these regulations, the petitioner shall be required to demonstrate whether or not these suspicions are true. The need for, and the depth and breadth of, studies required to demonstrate this effect must be specified on a case-by-case basis.

The procedure required is fourfold: (i) Establishment of normal background levels (or "norm") of the endogenous compound of carcinogenic concern in the target animals; (ii) determination of the effects of the sponsored compound on the norm; (iii) establishment of safe conditions of use of the sponsored compound by demonstrating how the compound can be used in a way that assures that the norm is restored in the target animals before slaughter; and (iv) development and validation of a practical assay to measure the endogenous compound at levels determined to be normal. The regulations specify how each of these steps is to be accomplished.

D. Specific Steps Required

The petitioner shall first be required to determine experimentally the normal background levels, or norms of the potentially carcinogenic endogenous compounds of concern in untreated target animals. A norm must be specific for the target animals and for the intended conditions of animal husbandry, and must include the effects of age, sex, breed, and geographic location. The sponsor shall

01159

provide the norm in the form of a curve of cumulative frequency distribution of untreated target animals over the observed levels of the endogenous compound. The curve shall also include 99 percent confidence bounds (Plate III appearing in § 500.89).

The median and shape of the frequency distribution must be known so that shifts in the norm can be measured. For this reason, the assay used to determine a norm must yield values for the endogenous compound different from zero for at least two-thirds of the untreated target animals. This latter requirement will permit calculation of the median and frequency distribution with a high degree of reliability, while recognizing the practical limits of technology. Morever, because the area of interest is that around the median, the requirement does not compel the petitioner to gather unnecessary data since the values at the lower end of the distribution are irrelevant.

The sponsor shall then determine the effects of the sponsored compound on the norm, and shall provide data on the postexposure decay of any observed increases in the norm. The norm shall be considered restored when the distribution of values for the endogenous substance of concern observed in a group of treated animals is with 99 percent confidence the same as the norm.

The norm, as defined, takes into account those variables that affect background levels. The final regulations thus attempt to respond to those comments suggesting that "normal background levels" would be difficult to define.

E. ENDOGENOUS MARKER RESIDUE; CALCULATION OF R_m

If the norm of an endogenous substance of carcinogenic concern can be increased by the administration of a sponsored compound, the endogenous substance can become an endogenous marker residue, i.e., its presence above certain levels can be considered an indicator of potentially carcinogenic residues in food. Approval of the use of such a sponsored compound shall be contingent upon the petitioner's furnishing data demonstrating that the norms are restored in the target animals before slaughter, and upon the availability of a practical assay that can reliably measure the endogenous marker residue in target animals. Such a regulatory assay must be capable of measuring the marker residue at the level, R_m, corresponding to the 33d percentile of the norm (Plate III set forth in § 500.89).

The R_m for an endogenous marker residue derives from an entirely different conceptual approach to safety than that used for the derivation of an R_m for an exogenous marker residue. To monitor shifts in the norm, the Commissioner must be able to measure the median and to determine the shape of the distribution. An assay capable of measuring the 33d percentile of the norm, and levels above this, provides the required analytical capability. The same assay evaluation criteria apply to endogenous compounds as to other compounds covered by these regulations.

Accordingly, the Commissioner has revised the regulations, which as proposed, would have established the lowest limit of reliable measurement at the 99th percentile of the norm. As the comments noted, an assay that can measure only the upper 99th percentile would not be able to detect many shifts in the norm, which is its primary function. The final regulations require an assay capable of a lowest limit of reliable measurement of the 33d percentile of the norm, which will readily detect any shifts in the median or mean of the norm. Actual monitoring, which is performed by the Animal Plant and Health Inspection Service of the United States Department of Agriculture, may occur at or above the 50th percentile of the norm but such monitoring will detect violative residues and detect significant shifts in the norm.

F. ALTERNATIVE PROCEDURE

Comments contended that an alternative to the foregoing procedure should be available for regulating endogenous substances. It was suggested that a tolerance for an endogenous compound can be established, even at levels above the norm, provided appropriate toxicity testing on the compound is carried out and a safe level can be established in accordance with parts IV through VII of the preamble and §§ 500.84 through 500.90 (21 CFR 500.84 through 500.90). Separate mechanisms with distinctly different rationales have been developed to measure compliance with the no-residue standard of the act for endogenous and exogenous compounds.

As noted earlier, for exogenous compounds the regulations require development of an assay with a minimally acceptable lowest limit of reliable measurement at or below the level needed to assure that any undetected residues pose essentially no increased risk of cancer in the population. Moreover, should a new assay with a lower limit of reliable measurement be developed at a later time that will satisfy the essay evaluation criteria, that assay will be adopted by the Commissioner. On the other hand, the method for measuring compliance with the no-residue standard for an endogenous substance is based on calculation of the norm, a calculation that is independent of and probably unrelated to the lowest limit of an appropriate assay's reliable measurement. The Commissioner concludes that monitoring of changes in the norm is the best available method for regulating the use of compounds that may increase pools of potentially carcinogenic endogenous substances, and rejects the suggestion that a tolerance for such compounds be established. The Commissioner would be receptive to suggestions for alternative mechanisms of control, but until an acceptable alternative is identified, all such compounds will be required to comply with the requirements imposed by §§ 500.89 (c) through (e) and 500.90.

VIII. REGULATORY ASSAY: EVALUATION CRITERIA AND APPROVAL PROCESS

A. INTRODUCTION

The Commissioner can approve a sponsored compound for use in food-producing animals only if the intended use of the compound does not result in the accumulation of potentially carcinogenic residues in edible tissues and if an assay is available that can reliably measure such residues at and above the R_m. The assay must also be suitable for monitoring food from animals administered the compound to prevent food from reaching the marketplace if it is adulterated with potentially carcinogenic residues resulting from misuse of the compound.

Several comments argued that the proposal would discourage the search for better assays, and that this was not in keeping with the intent of the cancer provisions of the act. Further, some comments contended that FDA should only be concerned with the approval of assays that avoid false negative results and that any detected residue should be investigated to determine its identity. Other comments proposed that when more "sensitive" assay methods (i.e., assays with still lower limits of reliable measurement) are developed, the assays should only be used as screening tests and that the required "sensitivity" (or safe level) derived from the statistical analysis of animal carcinogenesis data should be retained for regulatory action. These comments argued that unless new biological information warrants a change in assay "sensitivity," new regulatory assays should not be adopted. Comments stated that the efforts to increase "sensitivity" had to be balanced by the need to assure the practicability of an assay for regulatory use, the desirability of avoiding false negatives, and the importance of reproducibility of results. These comments implied that, given these countervailing concerns, more "sensitive" assay methods should not be adopted because the proposed statistical treatment of carcinogenesis data is sufficiently conservative to protect the public health.

Still other comments suggested that more practical methods should be approved for purposes of screening which would accept a low level of false positives with a high degree of assurance that false negatives would not occur. Confirmatory methods, which would undoubtedly require more time for cleanup of samples and greater instrument specialization, should then be used to provide evidence that can withstand legal scrutiny. Some comments stated that certain reagents and instruments required for an assay may not be readily available because of their unique applicability. They suggested that the regulation be changed to allow sponsors to supply such items when necessary. One comment pointed out that the word "control" in the phrase "well-equipped analytical control laboratory" connotes a highly specialized laboratory which is unlikely to have the necessary instrumentation for residue analysis, and hence urged that it be deleted.

01160

Because the assays required by these regulations are to be used for regulatory monitoring of residues of potential carcinogenic concern in human food, the Commissioner concludes that rigorous criteria must be established for approval of these assays. Furthermore, a proposed assay must be subjected to an objective evaluation to determine if it meets the criteria. Only then can the Commissioner assure that an assay will provide a reliable and practical monitoring device to prevent violative residues in food. Many comments in essence contended that more explicit criteria and evaluation procedures should be specified, and the Commissioner concurs with these comments.

Any assay is characterized by a set of attributes which determine its quality: dependability, practicability, specificity, accuracy, and precision. These regulations specify objective criteria for these attributes. A proposed assay must be shown to meet these criteria during study in a single laboratory and also in interlaboratory study in government regulatory laboratories. The latter requirement is essential, because the assays are to be used in several regulatory laboratories (FDA, USDA, and State laboratories), and the Commissioner must determine in advance that an assay will perform in more than one such laboratory. The regulations specify that the interlaboratory validation study shall be carried out in those laboratories (USDA and FDA) that will be using the method in surveillance and enforcement programs.

The steps in obtaining approval of an asay are: (i) Assay development and study by the petitioner to determine if the assay satisfies the acceptability criteria; (ii) FDA review of the petitioner's study to determine suitability of the assay for evaluation in interlaboratory study; and (iii) interlaboratory validation study, again approval contingent upon satisfaction of acceptability criteria.

B. SOURCES OF DATA TO SUPPORT THE ASSAY

Data from studies of an assay using three types of samples are necessary to support approval. The petitioner must prepare samples of target tissue to which known amounts of marker residue are added ("spiked" tissues), and compare responses obtained from assays using these tissues with responses obtained from assays of target tissues known to be free of marker residues (control tissues). In constructing an analytical curve from these data and determining its 99 percent confidence limits (plot of observed response versus concentration of marker residue), as many samples as possible should be run, preferably by different analysts, for interlaboratory validation of the assay will eventually be required. The variability among different analysts can be determined at the developmental stage and adjustments made before the assay is submitted for FDA review.

A petitioner should also be satisfied that the assay meets all of the evaluation criteria and also that it is consistent with general principles of good analytical practice before submittal for FDA review. Past experience shows that a petitioner's failure to follow good analytical practices during initial assay studies often results in interlaboratory failure even though the initial results may appear satisfactory during a paper review of the assay by FDA. A petitioner should assure that no results enter the construction of an analytical curve when it is known that the results were obtained using other than acceptable principles of analytical practice.

In addition to the spiked tissue tests, a petitioner must also submit data showing the applicability of the proposed assay to target tissues taken from target animals treated with the sponsored compound ("dosed" tissues). To validate the assay, dosed tissue samples are required that contain the marker residue at a level approximating R_m. A standard curve must also be submitted, constructed by taking the marker residue of known purity at different concentrations, determining the response, and plotting the relationship.

C. SUBMISSION OF DATA

Agency resources for reviewing and validating assays are limited. The Commissioner therefore has established a precise format for submitting the data to support acceptance of an assay. It is a well-recognized principle, applied both by the courts and administrative agencies, that a standard format can be required for pleadings, requests for licenses, and other applications. This format may also designate special types of information that must be contained in the submission. Therefore, the agency will refuse to accept a petition or review an assay when the request for approval fails to conform to the format outlined below.

1. *Assay description and petitioner's evaluation.* The petitioner must provide a complete description of the assay to allow FDA to determine whether it is potentially acceptable. Because this threshold determination of acceptability will trigger an extensive interlaboratory validation procedure, the Commissioner concludes that the discussion must be sufficiently rigorous to minimize waste of agency resources. Therefore, the submission must discuss in detail:

(a) What equipment and reagents are necessary;

(b) How the assay is performed; and

(c) How the assay complies with the dependability, practicability, specificity, accuracy, and lowest limit of reliable measurement criteria prescribed in § 500.90(d) (21 CFR 500.90(d)) and discussed under paragraph VIII. E. below in this preamble.

2. *Data.* The data and worksheets, including spectrograms, chromatograms, etc., from the spiked tissue, dosed tissue, and control tissue analyses are also necessary for the preliminary review of the assay to determine whether it actually complies with the evaluation criteria.

D. FDA REVIEW

The Commissioner will conduct a paper review of a petitioner's submission to determine whether an assay complies with the acceptability criteria. These regulations generally alert potential petitioners to the applicable statutory standards and criteria, which should permit a petitioner to assess preliminarily the acceptability of an assay before filing a petition, and thereby reduce the agency's workload.

If on preliminary review an assay appears to comply with the evaluation criteria, it will then be subjected to the interlaboratory assay validation study to determine whether it is indeed a practicable and reliable regulatory tool. Should the initial review establish that the assay fails to meet these criteria, the petition will be denied. A conclusion that an interlaboratory assay validation study should be initiated, however, in no way guarantees that a proposed assay will be eventually approved.

E. ASSAY ATTRIBUTES AND ACCEPTABILITY CRITERIA

An assay must meet the following attributes and criteria:

1. *Dependability.* Dependability is the attribute denoting the likelihood that the proposed assay will yield no result because of uncontrollable features inherent in its design. Almost all assays will, on occasion, fail to yield any result. Often this occurs because of mishandling by the analyst, but sometimes failure may be the result of some aspect of the assay itself that may have been inadequately studied and defined or that cannot be controlled. For example, assays depend upon the availability of a standard against which measurements are compared. If the integrity of the standard depends on certain environmental factors (e.g., purity of the solvent in which it is maintained, temperature, light intensity, etc.) and these factors are understood, it may be possible to prevent assay failure. If this dependence is not known, however, the assay may fail and, depending on the sensitivity of standard integrity to the environmental factor of importance, may fail often. In this example, failure can mean a highly inaccurate result, assuming some fraction of the standard's integrity is retained, or it can mean no result at all, assuming complete loss of integrity.

The Commissioner concludes that assays used to monitor carcinogenic residues in food must be free of such uncontrollable features, and failure of a proposed assay to yield results during the petitioner's assay development studies or interlaboratory validation study can be a cause for refusing to accept the assay and for denying the underlying petition. Accordingly, the regulations require a petitioner to record and furnish all the information on, and provide an explanation of, runs of the developed assay that are begun, but never finished.

2. *Practicability.* The regulation under § 500.90(d)(2) defines the practicability attribute as follows:

01161

The assay shall be considered practicable only if it is suitable for routine use in a government regulatory laboratory. The time required to complete the assay must be consistent with regulatory objectives (monitoring, compliance, etc.). All supplies, equipment, reagents, standards, and other materials necessary to conduct the assay must be commercially available except that reference standards may be supplied by the petitioner if they are not commercially available. The Commissioner will withdraw approval of any assay method and initiate regulatory action against the sponsored compound, if the petitioner breaches such a condition of the compound's approval.

An assay must possess no characteristics that may counteract the purpose for which it is developed. Accordingly, the Commissioner has established criteria for practicability in terms that relate specifically to the nature of the laboratories in which the assay will be used (i.e., regulatory laboratories where time and availability of equipment and reagents are critical factors in their ability to perform satisfactorily the mandated functions).

The inability to use an assay at a regulatory laboratory because a needed reagent is not readily available or because excessive time is required to complete the assay presents potential risks to public health and cannot be sanctioned. Obviously, some assays will require some unique items, particularly reference standards. The Commissioner agrees with comments suggesting that as long as a sponsor makes reference standards available to all persons having an interest, the requirements of the regulation will be met. A commitment to supply reference standards when they are not commercially available may be made a condition of the sponsored compound's approval, and failure to supply the government or other laboratories as required is a basis for withdrawing a compound's approval. The Commissioner concludes that an assay is not practical if it is dependent on the use of any other unique equipment or materials that are not commercially available.

3. *Specificity.* The regulations specify that for an assay to be accepted, an observed response must without question be due to the compound being measured and that compound only. It is a fundamental part of the development of an assay to determine whether or not it possesses this important attribute. Among analytical chemists and biochemists, an "assay" that does not demonstrate this attribute is of little value, and indeed, in a regulatory setting, such an assay could be dangerously misleading. For this reason, the Commissioner has established rigorous specifications for this attribute.

In general terms, specificity describes the uniqueness of the relationship between the observed effect (or response) and the applied stimulus (in this case the chemical under analysis). In analytical chemistry and biochemistry, the term specificity is commonly used in reference to the uniqueness of a response resulting from the application of a stimulus having specific characteristics; that is, the term has a qualitative dimension only in that it does not relate to either the quantity of response or stimulus or to the nature of the relationship between response and stimulus. Both of the latter criteria, which might also be considered aspects of specificity, are central to good analytical practice. The regulations consider both the qualitative and quantitative aspects and groups them together under the general attribute of specificity. The Commissioner's objective is to assure that, whatever the observed response, it is uniquely related to the marker residue both qualitatively and quantitatively. The establishment of an analytical curve (not simply a standard curve, but one derived from actual measurements obtained on tissue samples containing known amounts of marker residue at different levels and from control samples) provides the means to determine whether the responses produced by an assay are single-valued, as they must be if an assay is to be considered fully specific. Only assays that yield continuously increasing or decreasing analytical curves will satisfy the criterion of single-valuedness.

Finally, the regulations require that the assay contain a sufficient number of independent measurements utilizing independent physicochemical principles to assure specificity (i.e., the identity of the marker residue must be confirmed). There may be many ways in which specificity can be demonstrated experimentally. A petitioner may use highly sophisticated research tools to demonstrate that a proposed assay is specific in the senses discussed above. However, a regulatory analyst, using an approved assay, must have at his disposal some technique (again capable of meeting other criteria) which can provide assurance that an observed response is due to the marker residue. At present, mass spectroscopy is probably an ideal choice for acquiring the requisite specificity, although there are other possibilities. Some determinations (e.g., those requiring enzymes) may have an inherent high specificity, but others have low specificity (e.g., gas, thin-layer, and liquid chromatography) and require other, independent, types of measurements to achieve the requisite confirmation of identity. By adopting this definition of specificity, the Commissioner concludes that all concerns expressed in the comments over "false positives" or "false negatives" are moot.

4. *Accuracy.* Assays yield measurements of concentration that are in some proportion to the true concentration of the compound being measured. The accuracy of an assay is expressed as a percent of the compound's true concentration. The regulations prescribe a specific accuracy criterion: The averages of the observed responses must fall within 60 to 110 percent of the true value. The criterion is consonant with current, good analytical practice and is based on agency experience with methods that are routinely used for trace analysis.

5. *Lowest limit of reliable measurement* (L_m). To be accepted for regulatory purposes, an assay must be able to distinguish, with a very high degree of certainty, target tissues that contain levels of the marker residue at or above R_m from target tissues that do not. This distinction must be reproducible and capable of supporting legal action when violative residues of the sponsored compound occur.

To provide the necessary degree of discrimination, the regulations require that the assay be capable of producing a response when the marker residue is present in target tissue at or above R_m that is, with 99 percent confidence, different from the response in nontreated (control) target tissue (i.e., the difference between the responses of control target tissue and target tissue containing the marker residue in target tissues at or above R_m is, with 99 percent confidence, greater than zero). The actual lowest limit of reliable measurement, L_m, will be determined by reference to the analytical curve of the proposed assay. If the determined lowest limit of reliable measurement, L_m, of the proposed assay is at or below the R_m as determined in accordance with paragraph VI.B.3. or paragraph VII.E. of this preamble, this criterion shall be considered satisfied. This procedure tests the critical factor of assay precision. Thus, an assay that satisfies this criterion will provide a reliable regulatory tool to enable the Commissioner to discriminate safe from unsafe food.

An assay that satisfies this criterion will often have a high signal-noise ratio, although this ratio may be a function of the fluctuations in the equipment used to conduct the assay. The mechanism established by the regulations is geared to the assay's variability; if the assay yields readily reproducible results, the importance of determining the signal-noise ratio is diminished. Every regulation has a zone of ambiguity, however, and the Commissioner believes that it is not now appropriate to define more precisely this requirement for an assay's approvability. In such instances, the professional judgment of the reviewing scientist will come in to play within prescribed limits. Sophisticated methods of statistically analyzing the results of assays offer the promise of more refined standards for this criterion that will take into account assay variation and yet yield the high degree of confidence in assay results, e.g., regression analysis of the spiked tissue, dosed tissue, and tissue blank results. The agency, in conjunction with the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture (APHIS), will be developing in guidelines for further refining this criterion and may subsequently propose amendment of the regulations to prescribe precise standards for evaluating assay accuracy.

The Commissioner recognizes that the term "method sensitivity" is widely used to describe the lowest level of a compound under analysis which can be detected as measured with an analytical assay. Indeed, the original proposal used this term to describe what in the final order has been termed "the lowest limit of reliable measurement." However, there is some confusion surrounding the term "sensitivity," which derives in part from the fact that the term has been

01162

used in two senses: (1) As the lowest level of a compound which can be detected by an assay; and (2) as the lowest level of a compound which can be measured reliably by an assay. In fact, the correct meaning of the term "method sensitivity" is unrelated to a particular level of compound concentration, but rather relates to the ratio of change in instrument response to the change in compound concentration. The term "sensitivity" has therefore been dropped from the final regulations. The Commissioner has adopted the term "lowest level of reliable measurement" because that term more precisely describes the attribute.

In response to comments urging that any "detected residue" should be subject to regulatory control, the Commissioner points out that it is an inherent characteristic of almost all analytical methods that compounds can sometimes be detected at levels below the levels at which they can be reliably measured. More precisely, detection of a compound simply means that there is some instrument response above background levels which could be the compound of interest, but this response cannot be considered as a reliable measurement of the compound. Since protection of public health is the issue, the Commissioner must be in a position to document conclusions based on analytical data, often in a court of law. A major aim of these regulations is to assure that assays used to obtain such data can reliably measure residues. Hence, the Commissioner concludes that the discriminant for samples containing potentially violative exogenous marker residues shall be the lowest limit of reliable measurement, L_m, of the approved assay. Moreover, by imposing these criteria at the preapproval stage, the Commissioner will provide an added measure of public health protection by barring potentially unsafe compounds from the market place.

F. INTERLABORATORY VALIDATION OF ASSAY.

Although FDA will review the assays for each sponsored compound, the actual regulatory field screening of foods of animal origin will be primarily performed by APHIS, pursuant to the Meat and Poultry Products Inspection Acts, and by the States pursuant to the Public Health Service Act. The Food and Drug Administration performs a complementary regualtory function: followup analytical and field investigations of violative residues to assemble evidence for use in regulatory actions.

The initial paper review by FDA of material in a petition permits the agency to make a threshold determination of the acceptability of an assay. Adequate protection of the public health, however, requires assurance that these assays will function in the Government's regulatory laboratories. Therefore, these regulations also prescribe the procedure that will be used to assure that an assay is appropriate for use as a regulatory tool by Government laboratories.

The Commissioner will require that three Government laboratories (two FDA facilities and one USDA facility) independently validate an assay before he can determine that use of a sponsored compound can be approved. The delicate nature of the assays, their importance in assuring that no residues of carcinogenic concern will occur in food of animal origin, and the practical limitations on the Government's capacity to monitor food production and distribution make this requirement mandatory. These three laboratories must study an assay sufficiently to assure that the conclusions about its acceptability drawn by the petitioner in his submission are correct and that all criteria are met.

G. CONCLUSION

If an assay complies with the criteria described above and prescribed by the final regulations, and compliance can be verified under actual conditions of regulatory use, the Commissioner will approve the assay. A full description of the approved assay will be published in the FEDERAL REGISTER upon approval of the petition, in accordance with the provisos to the anticancer clauses and section 512(i) of the act.

IX. WITHDRAWAL PERIODS

A. INTRODUCTION

The regulations define the withdrawal period for a sponsored compound as the time required, after cessation of target animal exposure to the sponsored compound, for the marker residue to deplete to L_m in the target tissue. The withdrawal period must also be compatible with actual conditions of livestock management and reasonably certain to be followed in practice. Because of the way in which the regulations define marker residue, target tissue, and L_m, the use of a sponsored compound in accordance with the prescribed withdrawal period will assure that no carcinogenic residues of such compound will be present in human food derived from treated animals. At any point after cessation of exposure but prior to the determined withdrawal period, treated animal tissues must be considered as containing residues of carcinogenic concern. Thus, the withdrawal period specifies the length of time after the last treatment with a sponsored compound in which animals shall not be slaughtered for food and during which milk shall be discarded.

Several comments addressed the procedures for establishing posttreatment withdrawal periods. Some contended that the requirement for tissue equilibration with residues in the experimental procedure for establishing withdrawal times was inappropriate for therapeutic drugs. Other comments suggested that the withdrawal periods be established to assure the absence of residues from edible tissues only, since they are the ones destined for human consumption. Finally, some comments expressed concern about the practicality of applying confidence-interval techniques to establishing withdrawal periods, especially when dealing with large animals.

B. DATA TO SUPPORT WITHDRAWAL PERIODS

The depletion studies required by the regulations to establish withdrawal periods must take into account the biological variability among animals and other variables that may influence depletion times.

Residue depletion studies must be conducted under conditions of the sponsored compound's maximum proposed use. If a petitioner can demonstrate target tissue equilibration with the marker residue, however, a shorter period of administration of the maximum dose can be permitted. The conditions of the study must also simulate actual use practice. That a compound is intended for a therapeutic use is irrelevant, because the function of this study is to determine the safe withdrawal period, regardless of the compound's intended mode of use. The proposed regulatory assay must be used to measure the marker residue in the target tissue, including milk and eggs where appropriate, because it is this assay that will be used for regulatory monitoring.

All raw data and evaluations must be submitted with the petition along with a graphical presentation of the tissue depletion curve (concentration of marker residue in target tissue versus time).

The analysis of the data must include the estimated depletion curve, which in most instances can be adequately approximated by a first order decay process. The upper 99 percent confidence bound will be determined for the samples from individual target animals and the time of intersection of this upper 99 percent confidence bound with the L_m value will be determined. The withdrawal period is the interval of time between the last administration of the compound and the time of intersection of the upper 99 percent confidence bound on the observations and the L_m of the approved regulatory assay, plus an additional interval determined by rounding out this time interval to provide a practical withdrawal period compatible with animal management practices.

For example, if the time of intersection of the upper 99 percent confidence bound on the individual tissue determinations and the L_m for the marker residue is 39 hours, the withdrawal period (preslaughter interval) would be established as 2 days. In the case of milk samples, if the time of intersection were 63 hours, a withdrawal time of 72 hours (discard of 6 milkings) would be established.

The use of a compound could not be approved if the necessary withdrawal period exceeds a period that is compatible with animal management practices. For example, the use of a compound in lactating animals will not be approved if the required withdrawal time for milk exceeds 96 hours (4 days) because the economics of milk production make observance of such discard times unlikely, or at least not reasonably certain, to be followed in practice.

When the marker residue is an endogenous compound, the withdrawal period is the time after cessation of ad-

01163

ministration of the sponsored compound required for the norm to be restored, with 99 percent assurance, extended if necessary to be compatible with conditions of livestock management. The validated regulatory assay must be used to collect this information.

C. RATIONALE FOR USING THE CONFIDENCE BOUND APPROACH

To establish that carcinogenic residues are absent from edible tissues of food-producing animals treated with the sponsored compound, the Commissioner must have information about the rate of residue depletion and the inherent metabolic variabilities among individual target animals, Confidence bounds on experimental data are the only means to allow prediction, with a given degree of confidence, of what will occur in the total target animal population. The Commissioner has prescribed 99 percent confidence bounds throughout these regulations as the degree of confidence necessary to assure protection of public health.

X. WAIVER OF REQUIREMENTS

The regulations permit the Commissioner, in response to a petitioner's request or on his own initiative, to waive, in whole or in part, any of the foregoing requirements for the scientific evaluation of sponsored compounds that have the potential to contaminate human food with residues whose consumption could engender a human risk of carcinogenesis. When an agency particularizes a statutory standard of conduct by regulation, due process requires that it permit affected parties to demonstrate how their alternative mechanism satisfies the statutory standard, and why the regulation should then be waived in the public interest. "Weinberger v. Hynson, Westcott, and Dunning, Inc.," 412 U.S. 609, 620 (1973). Moreover, it has been long settled that an agency may adopt a rule shown to be appropriate for the generality of instances and leave the correction of injustices to applications by those concerned. "National Nutritional Foods Ass'n v. Food and Drug Administration," 504 F.2d 761, 784 (2d Cir. 1974). For these reasons, the Commissioner has expressly included the waiver provision. The Commissioner advises, however, that a waiver will be granted only in exceptional circumstances, and, as the regulation provides, the basis for any waiver must be extensively documented.

XI. IMPLEMENTATION

The proposal would have applied the requirements of the regulations to all new approvals (basic or supplemental) filed or approved after the effective date of the regulations. Prior approvals were to be dealt with on a class-by-class basis, beginning with known carcinogens, suspect carcinogens, and continuing through all compounds previously approved on the basis of zero tolerance. These were to be reviewed as part of the agency's general safety review for previously approved new animal drugs.

The final regulations apply to all new animal drug applications, feed additive petitions, and appropriate color additive petitions, including appropriate supplemental applications, submitted subsequent to the effective date of the regulations. In addition, the requirements of the regulations shall apply to all pending petitions and applications unless the Commissioner determines that compliance with the anticancer provisions of the act can be adequately assured by requiring completion of one or more of the required studies subsequent to approval. The criteria set forth in the regulations are based on generally recognized scientific principles for testing and evaluating chemical compounds for potential carcinogenesis requirements that Congress contemplated FDA would adhere to when it enacted the Food Additives Amendment of 1958 and the Animal Drug Amendments of 1968 (21 U.S.C. 348 (b) and (c) and 360b (b) and (d)).

The Food and Drug Administration has already applied these standards to compounds currently being evaluated for approval or subject to proposals to withdraw approval (e.g. diethylstilbestrol published in the FEDERAL REGISTER of November 2, 1976 (41 FR 52105) and the nitrofurans published in the FEDERAL REGISTER of May 13, 1976 (41 FR 19906) and August 17, 1976 (41 FR 34884)). Accordingly, all previously approved applications for compounds subject to the anticancer clauses will be reviewed as part of the general review of the safety of marketed animal drugs. When the agency finds deficiencies in the data supporting a prior approval, it will issue either a FEDERAL REGISTER notice or a letter pursuant to section 512(l)(1) of the act establishing the time within which the provisions of these regulations must be satisfied. For notices previously published or letters previously issued, the criteria of these regulations will be used to determine whether the data supporting applications are acceptable. The Commissioner will, however, immediately proceed to withdraw approval of applications on the basis of information indicating that a health hazard exists or that no studies necessary to bring a sponsored compound into compliance with the regulation have been conducted.

ADDITIONAL TIME FOR COMMENT

These final regulations largely reflect not only the proposal published in July 1973, but the current FDA practice in reviewing sponsored compounds. Comments on the proposal and petitions filed during the intervening 3 years have raised most of the issues discussed in this preamble and resolved in the final regulations. In the main, therefore, the regulations embody no new decisions. The DES proviso to the anticancer clauses is self-executing, and FDA has therefore been obligated to deal with the issues posed by carcinogenic compounds proposed for use in food-producing animals in the absense of regulations. Accordingly, the Commissioner concludes that these regulations shall become effective March 23, 1977.

Nevertheless, the Commissioner recognizes that it has been over 3 years since these regulations were proposed and that the final regulations resolve some issues not specifically dealt with in the proposal but raised by the comments. For these reasons, the Commissioner is providing an additional 60 days for any interested person to submit further comments on these specific issues. The Commissioner will evaluate any additional comments and will later publish any revisions to the final regulations, if appropriate.

The Commissioner urges that any comments submitted within this additional period address only new issues, and not reopen matters raised by the initial proposal and discussed in this preamble. The Commissioner is particularly interested in receiving comments on four specific areas of the regulations. First, he invites further discussion of the acceptable level of risk for use in the modified Mantel-Bryan calculation. At the present time, FDA is involved in administrative adjudications concerning potentially carcinogenic animal drugs. These proceedings may assemble additional evidence on the acceptable level of risk. Because this issue is important to application of the regulations, the Commissioner believes additional comment will contribute to public understanding. This action will in no way jeopardize the public health, for the administrative record adequately supports the current level of risk; the Commissioner is interested in comments on whether the level of risk should be further reduced.

Second, the Commissioner will entertain comments on the concept of comparative metabolism. This unique approach was developed in response to the diverse comments on the issue of which metabolites of a sponsored compound, if any, should be tested. An analogous procedure of the Environmental Protection Agency has received judicial approval. "Environmental Defense Fund, Inc., et al., v. Environmental Protection Agency," No. 75-2259, (D.C. Cir., November 10, 1976), slip op. at 14. The Commissioner welcomes suggestions for alternatives to this approach.

Third, as previously noted, the Commissioner invited suggestions for alternative mechanisms for dealing with endogenous compounds. Several comments on the proposal urged that an alternative procedure for evaluation of such compounds should be available, but failed to suggest any feasible approaches.

Finally, the Commissioner welcomes suggestions of refined mechanisms for statistically differentiating target tissue containing the market residue from blank target tissue.

The Commissioner concludes that all of the provisions of the final regulations should be implemented pending reconsideration of any specific provisions based upon additional comments. This will work no hardship since all provisions of the regulations are supported by the record, and, except for the level of risk, the only changes the Commissioner contemplates concern alternative methods of satisfying the statutory requirements.

The Commissioner has carefully considered the environmental effects of the regulations and, because this action will not significantly affect the quality of the

01164

human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

This final order was proposed prior to Executive Order 11821, requiring agencies in the executive branch to review regulatory and legislative proposals they initiate for inflation impact, and so does not require inflation impact review.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sections 402, 403, 409, 512, 701(a), 706, 52 Stat. 1046–1048 as amended, 1055, 72 Stat. 1785–1788 as amended, 74 Stat. 399–403, 82 Stat. 343–351 (21 U.S.C. 342, 343, 348, 360b, 371(a), 376)) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

PART 8—COLOR ADDITIVES

1. In Part 8, by amending § 8.36 by adding new paragraph (c) to read as follows:

§ 8.36 Application of the cancer clause of section 706 of the act.

* * * * *

(c) *Color additives for use as an ingredient of feed for animals that are raised for food production.* Color additives that are an ingredient of the feed for animals that are raised for food production must satisfy the requirements imposed by subpart E of Part 500 of this chapter.

PART 500—GENERAL

2. In Part 500, by adding a new Subpart E, consisting of §§ 500.80 through 500.98, to read as follows:

Subpart E—Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Edible Products of Animals

Secs.

AUTHORITY: Secs. 402, 408, 409, 512, 701(a), 706, 52 Stat. 1046–1048 as amended, 1055, 72 Stat. 1785–1788 as amended, 74 Stat. 399–403, 82 Stat. 343–351 (21 U.S.C. 342, 343, 348, 360b, 371(a), 376).

Subpart E—Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Edible Products of Animals

§ 500.80 Chemical compounds used in food-producing animals; procedures and criteria for determining the acceptability of assay methods for carcinogenic residues in edible products of such animals.

(a) *Purpose and applicability of this subpart.* (1) The act requires that compounds intended for use in food-producing animals shall be safe and that food produced from animals exposed to such compounds be safe for human consumption, and prohibits the use of any compound found to induce cancer when ingested by man or animal in food-producing animals unless it can be determined by methods of examination prescribed or approved by the Commissioner that no residue of such compound will be found in the food produced from such animals under conditions of use reasonably certain to be followed in practice. Petitions for the approval of the use of a compound in food-producing animals shall include adequate data for establishing the absence of residues of carcinogenic compounds in the food produced from such animals.

(2) The provisions of this subpart establish the following: (i) The lowest limit of reliable measurement for the regulatory assay required for carcinogenic residues by sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B) and sections 409(b)(2)(D), 512(b)(7) and 706(b)(5)(A)(iv) of the act;

(ii) The procedures and criteria for evaluation and approving such assays; and

(iii) The procedures and criteria for establishing the premarketing withdrawal period for use of compounds likely to produce such residues.

(3) This subpart shall apply specifically to compounds intended for use in food-producing animals and their feed that have the potential to contaminate human food with residues whose consumption could engender a human risk of carcinogenesis. The determination of this potential shall be based on considerations of chemical, biochemical, physiological, and toxicological data derived from the scientific literature and from other sources available to the sponsor or to the Commissioner and on the proposed patterns of compound use. The subpart establishes a sequential process for the collection of other chemical, biochemical, physiological, and toxicological data pertinent to the safety of the proposed use of the sponsored compound. This subpart shall not apply to essential nutrients.

(b) *General approach.* (1) When the Commissioner determine that a sponsored compound has the potential to contaminate food from food-producing animals with residues (the sponsored compound, metabolites, conversion products, or any other substances formed in or on food because of the compound's use) whose consumption may engender a human risk of carcinogenesis, the following procedure for data collection and evaluation shall become applicable:

(i) A metabolic study in the animals in which the sponsored compound is intended for use (target animals) designed to identify metabolites of concern;

(ii) A metabolic study of the sponsored compound in experimental animals designed to aid in assessing the carcinogenicity of residues that cannot practicably be tested individually (intractable residues);

(iii) Chronic testing in test animals to assess the carcinogenic potential of residues of the sponsored compound and to furnish data suitable for statistical treatment by the procedure of Mantel and Bryan, (Mantel, N., and W. R. Bryan, "'Safety' Testing of Carcinogenic Agents," "Journal of the National Cancer Institute," 27(2):455–470 (1971)) as modified by Mantel et al. (Mantel, N., et al., "Improved Mantel-Bryan Procedure for 'Safety' Testing of Carcinogens," "Cancer Research," 35:865–872 (1975)) [1] and by this subpart, to permit the no-residue requirement of the act to be operationally defined for purposes of establishing a lowest limit of reliable measurement for an assay to measure residues of the sponsored compound;

(iv) A detailed metabolic study of the sponsored compound in target animals designed to identify a specific residue and tissue to serve as indicators (marker residue and target tissue) to determine whether the no-residue requirement of the act is satisfied;

(v) Development of a regulatory assay to measure the marker residue in the target tissue at and above the level operationally defined as satisfying the no-residue requirement of the act; and

(vi) Establishment of the premarketing withdrawal period required for the safe use of the sponsored compound.

(2) If, at any point in the sequential process of data collection set forth in paragraph (b)(1) of this section, the evaluation of the data satisfies the Commissioner that no human risk of carcinogenesis attaches to the proposed use of the sponsored compound, the compound shall be considered for approval under the general safety provisions of the act.

§ 500.84 Metabolic study in target animals to identify residues for chronic testing.

(a) A metabolic study, described in paragraph (b) of this section, shall be conducted in target animals to provide data on the physicochemical characteristics of residues, their relative proportions, their distribution among the various edible tissues (which include milk or eggs when applicable), and their retention and depletion by the animals.

(b) The target animal metabolic study shall satisfy the following minimum requirements:

(1) The metabolic study shall be conducted in target animals with the spon-

[1] Copies may be obtained from: Associate Director for Scientific Evaluation (HFV-100), Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

01165

sored compound bearing appropriate radiolabels, unless other expermental methods permit equivalent measurement of residues. Such labels must assure that residues containing structural moieties of potential carcinogenic concern can be detected and measured in edible tissues at levels as low as the best available technology will permit. Hypotheses about the sponsored compound's projected metabolic pathways may be used as a guide to experimentation, but shall not be a substitute for actual experimentation.

(2) The dosing regimen shall be consistent with the maximum proposed use level and proposed duration of exposure to the sponsored compound. For a compound that is proposed for continuous or repeated use in target animals, administration for the metabolic study need continue only until residue equilibration or tissue saturation has been demonstrated.

(3) The metabolic study shall be designed to yield the following information:

(i) The concentrations and total number of residues detected in edible tissues of target animals immediately following cessation of exposure;

(ii) Except when the Commissioner specifies otherwise, the concentrations and total number of residues detected in edible tissues of target animals when the total residue burden has depleted for at least three half-lives; and

(iii) The physicochemical properties of the detected residues to identify compounds of potential carcinogenic concern.

(4) The results of the metabolic study shall be submitted in the form of a detailed report conforming to the standards required of scientific manuscripts submitted for publication in the journals of professional scientific societies such as the American Chemical Society and the American Society of Biological Chemists. In addition, all raw data shall accompany and be referenced in the report.

(c) If the Commissioner determines that a sponsored compound has potential to contaminate food with residues whose consumption engenders human risk of carcinogenesis, the petitioner shall be required to determine the carcinogenic potency of the sponsored compound and any of its residues that might be of public health concern because of chemical structure or persistence and concentration in edible tissues. Ordinarily, chronic testing of the sponsored compound and selected residues in experimental animals shall be the preferred means of assessing carcinogenic potency. (Section 500.85 describes an alternative means of assessing the carcinogenic potency of residues whose isolation or synthesis in sufficient quantities for chronic testing proves to be beyond the practical limits of current chemical technology (intractable residues) by establishing additional criteria for selecting test animal species/strains used to conduct chronic toxicity testing of the sponsored compound.)

§ 500.85 Criteria for test animal selection; comparative metabolic studies to aid in assessing the carcinogenicity of residues that cannot practicably be tested individually (intractable residues).

(a) The primary criterion for the selection of species or strains of test animals for chronic testing of the sponsored compound and any metabolites selected in accordance with § 500.84 shall be the suitability of the species or strain as a model for man.

(b) If one or more intractable residues are also selected for chronic testing based upon the metabolic study in the target animal, a secondary criterion for the selection of species or strains of animals for the testing of the sponsored compound shall be employed. Metabolic studies of the sponsored compound in the test animal species or strains deemed suitable for chronic testing by the primary criterion shall be conducted to determine if the intractable residues present in the tissues of target animals are also produced in the test animals. Chronic testing of the sponsored compound in a species or strain of test animals in which the residues produced are similar to the complement of residues in the tissues of the target animals shall be considered an appropriate method of assessing the carcinogenic potency of the intractable residues.

§ 500.87 Chronic testing.

(a) Chronic toxicity tests shall be conducted to assess the carcinogenic potential of the residues of the sponsored compound.

(1) The sponsored compound and any residues selected for chronic toxicity testing shall be subjected to oral, lifetime, dose-response studies in the test animal species or strains selected in accordance with § 500.85. Each of these studies must be designed to determine whether the test compound is carcinogenic. Protocols for these studies should be submitted to the Commissioner for review prior to commencing testing.

(2) The Commissioner will determine whether any of the compounds tested is carcinogenic on the basis of the results of these chronic toxicity studies and other available information. If this evidence is equivocal, the compound shall be classed as a carcinogen until further testing resolves any remaining questions regarding carcinogenicity.

(b) When the Commissioner determines that a sponsored compound has the potential to increase the normal levels (pools) of carcinogenic and potentially carcinogenic substances endogenous to the target animals, the petitioner shall meet the requirements of § 500.89 (c), (d) and (e).

(c) For each tested compound classed as a carcinogen, the appropriate data from the chronic dose-response studies shall be analyzed according to procedures described by Mantel and Bryan (Mantel, N., and W. R. Bryan, " 'Safety' Testing of Carcinogenic Agents," "Journal of the National Cancer Institute," 27(2):455–470 (1961)) and Mantel et al. (Mantel, N., et al., "Improved Mantel-Bryan Procedure for 'Safety' Testing of Carcinogens," "Cancer Research," 35:865–872 (1975)) [2]; subject to the modifications and restrictions set forth in paragraph (c)(1) through (9) of this section. The purpose of this analysis shall be to define the no-residue requirement of the act as it applies to the total residue of carcinogenic concern of the sponsored compound and thereby to determine the lowest level of reliable measurement that shall be required for a regulatory assay to be approved for the measurement of such residues.

(1) The administered dose of each test compound shall be expressed as a fraction of the total diet fed the test animal species/strains, e.g., parts per million, parts per billion, etc.

(2) The "safe" level of Mantel and Bryan, calculated for each test compound in accordance with this section, shall be expressed as a fraction of the total diet fed the test animal species/strains. It shall be calculated with 99 percent confidence for a maximum lifetime risk that is essentially zero but never expected to exceed 1 in 1 million.

(3) A slope of one probit per unit log dose shall be used for extrapolation to the "safe" level unless the experimental data indicate that a shallower slope is required to maintain the conservatism of the procedure.

(4) Data obtained from more than one dose level fed to groups of experimental animals of the same strain shall be combined as described by Mantel et al. (Mantel, N., et al., "Improved Mantel-Bryan Procedure for 'Safety' Testing of Carcinogen," "Cancer Research", 35:865–872 (1975)),[2] and subject to the restrictions specified by these authors.

(5) Pooling data from various chronic tests using different animal sexes, species, or strains shall be permitted if it can be demonstrated that the protocols are of compatible design. If statistically significant biological differences in tumorigenic responses are observed between sexes or among species or strains of experimental animals, only subsets of data representing statistically and biologically compatible bioassays may be combined for analysis.

(6) All tumors (benign and/or malignant) shall be considered in the analysis.

(7) The number of animals at risk may be adjusted for competing risks unrelated to the compound-induced carcinogenesis only when the data clearly support such an adjustment.

(8) When only the sponsored compound is subjected to chronic testing, the calculated "safe" level shall be designated at S_a. When more than one compound is subjected to chronic testing, the

01166

lowest of all calculated "safe" levels shall be designated S_s. S_s shall be expressed as the fraction of the diet fed the test animals (e.g., parts per million, parts per billion, etc.).

(9) The no-residue requirement of the the act shall be considered satisfied when conditions and use of the compound, including any required withdrawal period, can be prescribed to assure that the sum of the levels of all potential residues of carcinogenic concern will not exceed S_s in the total diet of man and a regulatory assay is available that is capable of reliably measuring such residues at and above that level. All residues of the sponsored compound shall be classed as carcinogenic except those that have been unequivocally shown to be noncarcinogenic.

(d) The S_s value represents the sum of all residues of carcinogenic concern that must not be exceeded in the total diet of man. For individual edible tissues, the value that must not be exceeded shall be designated S_m and calculated according to the following formula:

$$S_m = \frac{S_s}{T}$$

NOTE.—T is the fraction of the total daily diet of man represented by an individual edible tissue.

(1) The principal S_m calculations are as follows:

Edible tissue	T	S_m
Muscle	1/3	$3S_s$
Milk	1	S_s
Eggs	1/3	$3S_s$

(2) Calculation of S_m for tissues consumed less frequently than muscle may take into consideration the frequency of consumption of such tissues if it can be clearly shown that S_s will not be exceeded in the total human diet.

§ 500.89 Metabolic study to identify the marker residue and target tissue.

(a) The petitioner shall conduct a study of the metabolic fate of the sponsored compound in target animals adequate to provide the data necessary for the selection of a marker residue in target tissue.

(1) The target tissue is that tissue in which measurement of the total residue burden of carcinogenic concern is a reliable measure of the total residue burden of carcinogenic concern in all edible tissues.

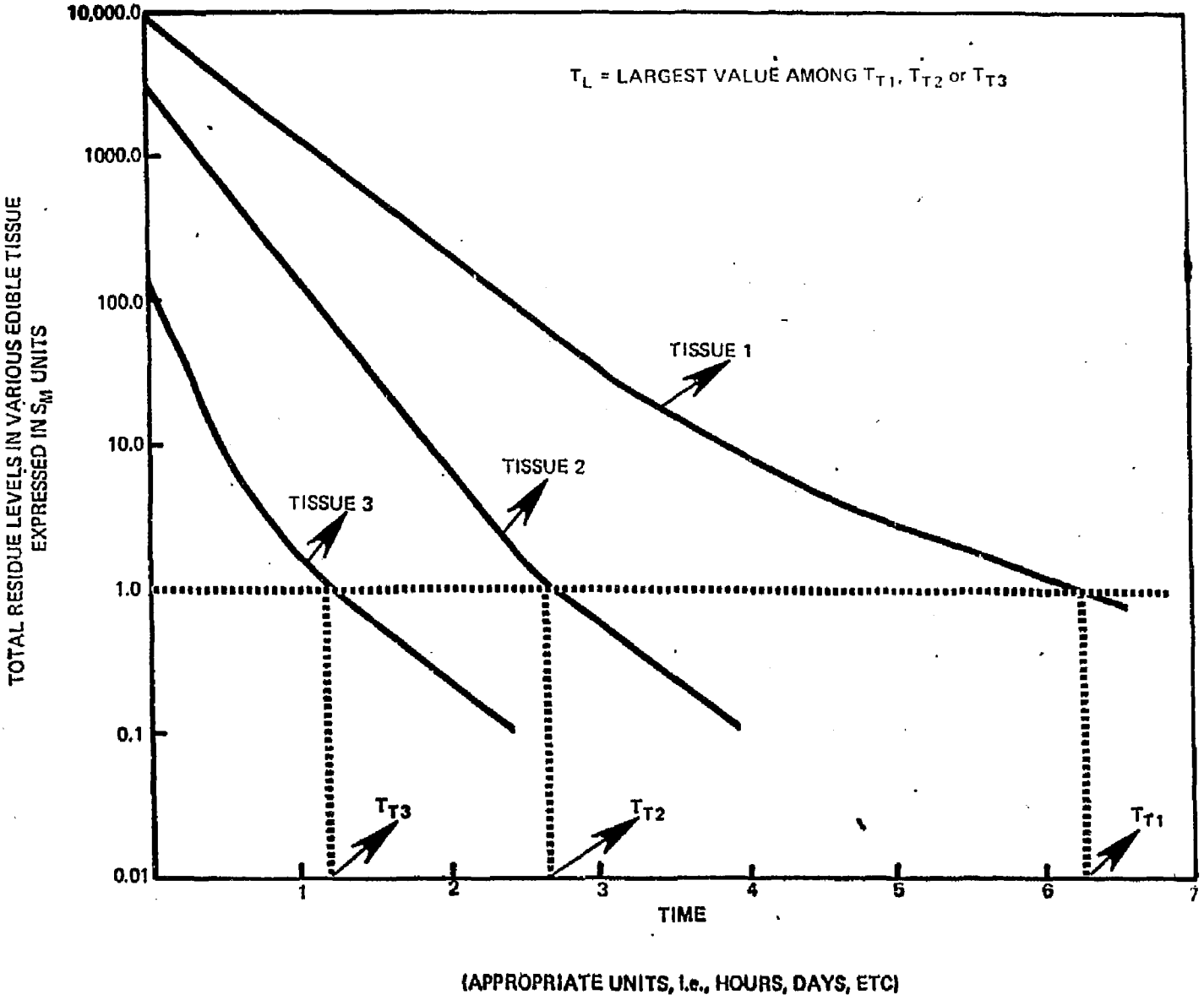
(2) The marker residue for the sponsored compound shall be that residue (the sponsored compound, any metabolite, or more than one of these) whose level in the target tissue is a reliable measure of the total burden of all residues of carcinogenic concern in all edible tissues.

(b) The metabolic study to establish the marker residue and target tissue shall comply with the requirements set forth in § 500.84(b) (2) and (4), with the following additional specifications:

(1) For each edible tissue, the depletion profile of the total residue of carcinogenic concern shall be constructed and shall include measurements of levels at least as low as the S_m appropriate to the tissue under study, set forth in Plate I as follows:

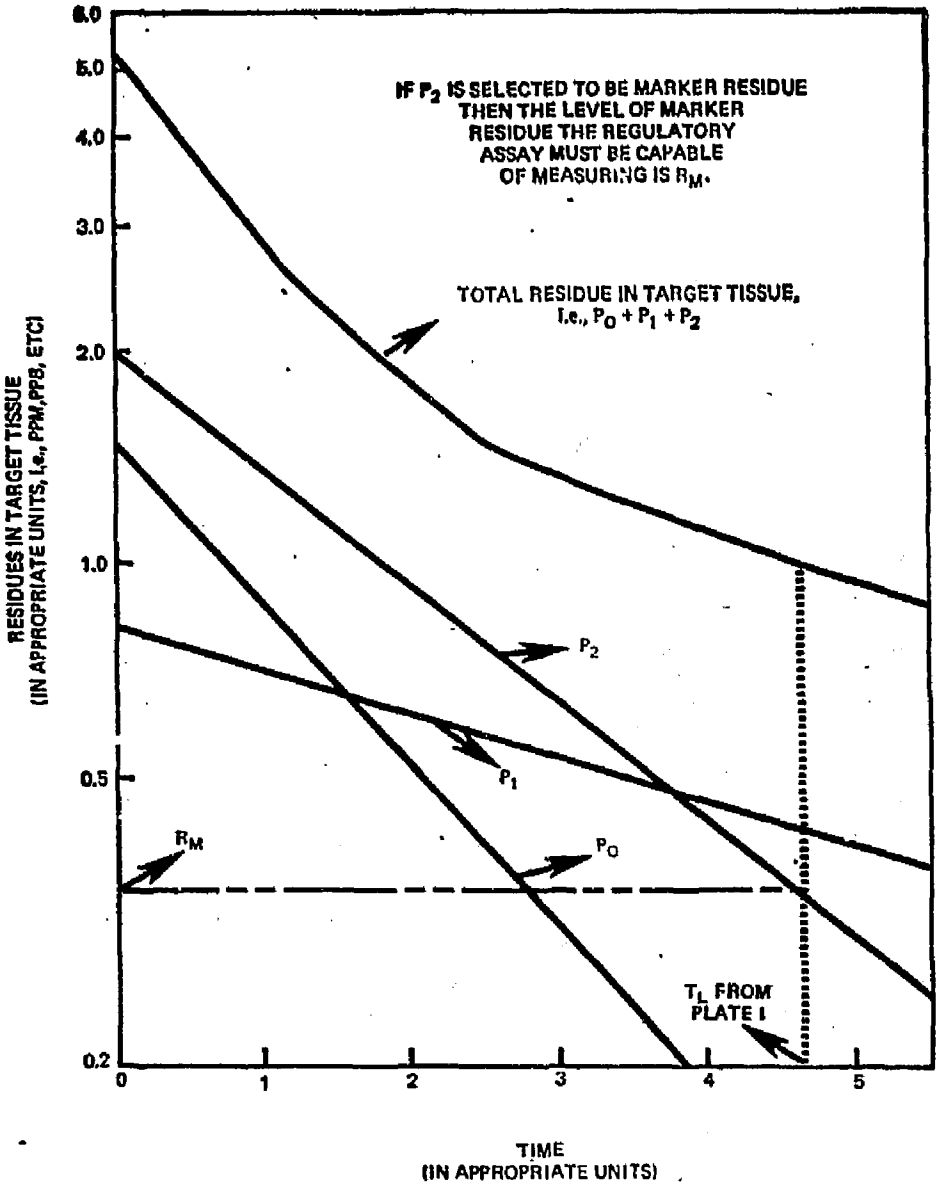
01167

PLATE I. RESIDUE DEPLETION CURVES TO BE USED IN THE DETERMINATION OF MARKER RESIDUE AND TARGET TISSUE.



(2) Depletion profiles for one or more potential marker residues shall be constructed as set forth in Plate II in this paragraph, and shall include measurements of levels corresponding to the time when the total residue level has reached S_m in the edible tissue requiring the longest time to deplete to S_m (T_L of Plate I in paragraph (b) (1) of this section).

PLATE II. SELECTION OF MARKER RESIDUE AND ITS LEVEL R_M THAT MUST BE MEASURED BY THE REGULATORY ASSAY.



(3) If these specifications have been met by the metabolic study required by § 500.84(b), a second metabolic study need not be performed to satisfy this section.

(4) From these data, the Commissioner will select a marker residue and target tissue, and he will also designate the required level of marker residue, R_m (set forth in Plate II in paragraph (b)(2) of this section), that regulatory assays must be capable of measuring in the target tissue. The selection of R_m shall be such that the absence of the marker residue in target tissue above R_m can be taken as confirmation that the total residue burden of carcinogenic concern does not exceed S_m in each of the various edible tissues and therefore that the total burden of carcinogenic concern in the human diet does not exceed S_0.

(c) When the Commissioner determines on the basis of available scientific information that a sponsored compound has the potential to increase the normal levels (pools) of potentially carcinogenic substances endogenous to target animals, the petitioner shall provide the following additional data:

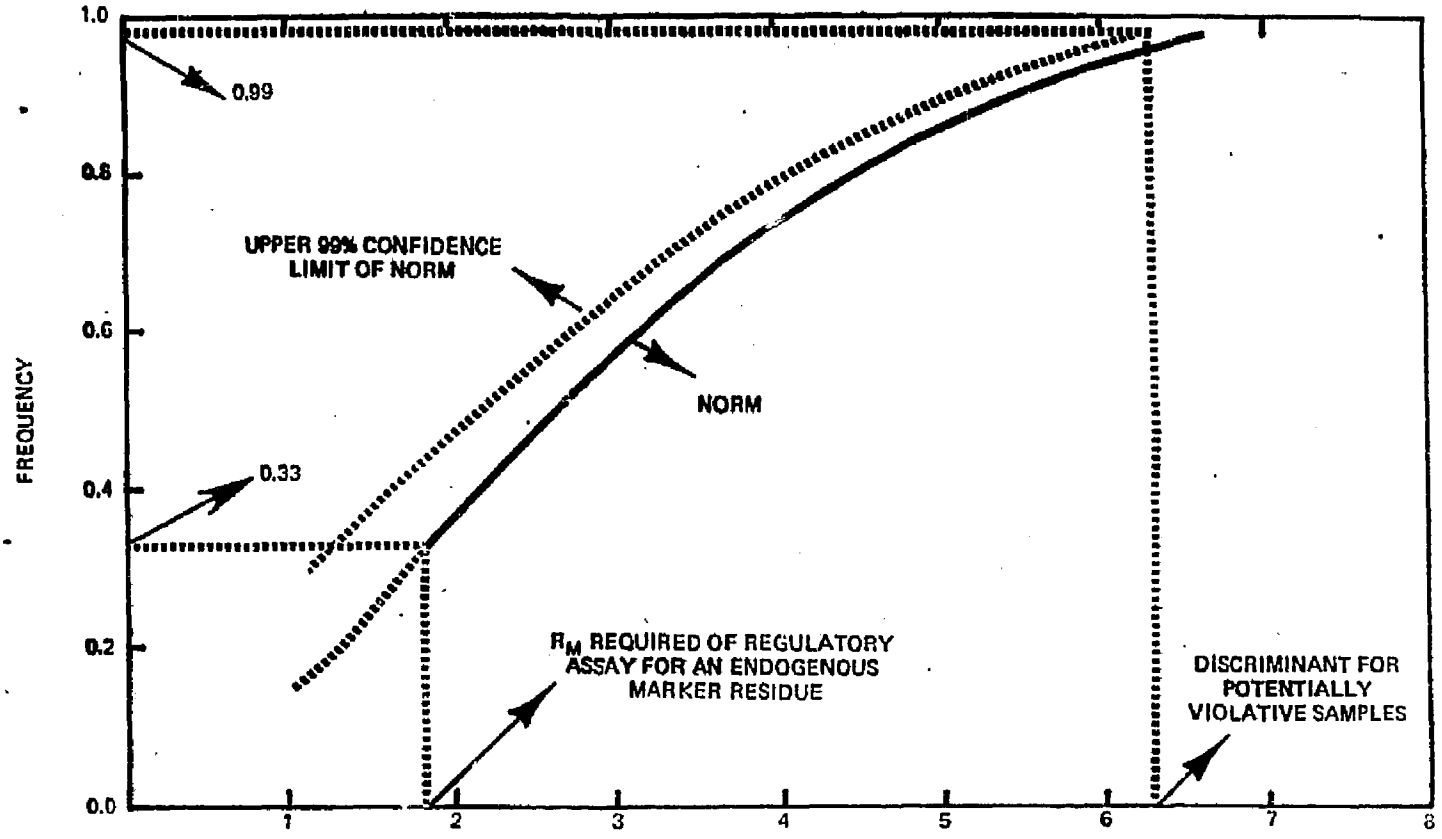
(1) An experimental determination of the background levels (norm) of each of the potentially carcinogenic endogenous substances of concern in untreated target animals.

(i) The norm shall be specific for the target animals and the intended conditions of animal husbandry, and shall be determined from studies designed to take into account differences due to factors such as breed, age, sex, state of estrus, and geographic location.

(ii) Each norm shall be submitted in the form of a graph of the cumulative frequency distribution versus the observed naturally occurring levels, including the 99 percent confidence bounds, set forth in Plate III as follows:

01169

PLATE III. SAMPLE OF A NORM



(iii) An assay shall be acceptable for the determination of a norm only if it yields values for the endogenous compound of interest greater than zero in at least two-thirds of the untreated target animals.

(2) Studies to measure the effect of the sponsored compound on the norm and the postexposure decay of any increase in the norm caused by administration of the sponsored compound.

(3) All data from these studies submitted in accordance with the requirements established in paragraph § 500.84(b)(4).

(d) For a potentially carcinogenic endogenous compound whose norm is increased by the administration of a sponsored compound, the no-residue requirement of the act shall be considered satisfied when the norm is restored.

(1) The norm shall be considered restored when the distribution of values for the endogenous substance of concern observed in a group of treated animals is with 99 percent confidence the same as the norm.

(2) The marker residue for a sponsored compound that affects a potentially carcinogenic endogenous substance shall be the affected endogenous substance.

(3) When the norm of more than one potentially carcinogenic endogenous compound is increased by administration of the sponsored compound, the marker residue for all endogenous compounds of concern shall be that endogenous compound whose norm requires the longest time for restoration.

(e) For an endogenous compound selected to be a marker residue, the required level of measurement, R_m, for the regulatory assay shall be the level of that endogenous compound corresponding to the 33d percentile of the norm, set forth in Plate III in paragraph (c)(1)(ii) of this section.

§ 500.90 Evaluation and approval of a regulatory assay.

(a) Before a petition can be considered for approval, the petitioner shall submit for evaluation and validation a regulatory assay developed to monitor compliance with no-residue requirement of the act. The regulatory assay shall reliably measure the marker residue in the target tissue at levels at least equal to and above R_m, as defined in § 500.89 (b) and (e). The criteria and procedures in paragraphs (b) through (g) of this section shall apply to the evaluation and approval of assays.

(b) The regulatory assay shall be evaluated and validated using data collected from three types of samples:

(1) Samples containing various known concentrations of marker residue added to the target tissue, i.e., "spiked" tissue samples.

(2) Samples containing various levels of the marker residue obtained from target tissue at appropriate time intervals after the sponsored compound is administered in accordance with the proposed labeling, i.e., "dosed" tissue samples.

(3) Samples obtained from untreated target animals, i.e., "control" tissue samples.

(c) The petition for approval of the proposed regulatory assay shall contain the following:

(1) A complete description of the assay.

(2) A list of all necessary equipment and reagents.

(3) A standard curve prepared from samples of the marker residue of known purity.

(4) An analytical curve of the observed assay response versus the tissue concentrations of the marker residue in spiked target tissue. The curve shall include the 99 percent confidence bounds of a single assay response.

(5) All raw data and worksheets from the analyses of spiked, dosed, and control tissue samples, and from the analysis used in preparing the standard curve, including spectrograms, chromatograms, etc.

(6) A discussion of the data generated in the assay development process pertinent to the evaluation criteria set forth in paragraph (d) of this section explain-

01170

ing how the data show that the proposed assay conforms to those criteria.

(d) A regulatory assay must satisfy the following criteria:

(1) *Dependability.* The assay shall be considered dependable if it does not result in an unreasonable number of failures due to unknown, uncontrollable, or random factors. Evaluation of the data to support the dependability criterion will be based on the total number of assay runs that are started to provide data points for the analytical curve of paragraph (c) (4) of this section. An explanation shall be required for any assay run started that yields no final determination.

(2) *Practicability.* The assay shall be considered practicable only if it is suitable for routine use in a government regulatory laboratory. The time required to complete the assay must be consistent with regulatory objectives (monitoring, compliance, etc.). All supplies, equipment, reagents, standards, and other materials necessary to conduct the assay must be commercially available except that reference standards may be supplied by the petitioner if they are not commercially available. The Commissioner will withdraw approval of any assay method and initiate regulatory action against the sponsored compound, if the petitioner breaches such a condition of the compound's approval.

(3) *Specificity.* The assay shall be considered specific if the observed response is a smooth and continuously decreasing or increasing function of the concentration of the marker residue and that compound only. The regulatory assay must be comprised of a sufficient number of independent measurements based on a different biological, biochemical, or physiochemical principles to assure that the identity of the marker residue is confirmed.

(4) *Accuracy.* The assay shall be considered accurate if the measurements it yields are normally no less than 60 percent nor greater than 110 percent of the marker residue's true concentration in the spiked target tissues.

(5) *Lowest limit of reliable measurement.* The regulatory assay shall be considered approvable if it can reliably discriminate with 99 percent confidence the marker residue response from the target tissue background response at or below the required lowest limit of reliable measurement, the R_m of § 500.89 (b) or (e). If the regulatory assay for an exogenous compound can reliably discriminate the marker residue response from the target tissue background response at a level below the required lowest limit of reliable measurement determined in accordance with § 500.89(b), the Commissioner shall approve the compound for use only under conditions that will not result in residues above that level.

(e) The Commissioner will review and evaluate the data submitted in accordance with paragraphs (a), (b), and (c) of this section. If the Commissioner concludes that the assay satisfies the evaluation criteria of paragraph (d) of this section, it will then be subjected to the interlaboratory validation study described in paragraph (f) of this section.

(f) Two Food and Drug Administration laboratories and one U.S. Department of Agriculture laboratory will independently run a number of assays to ascertain whether the regulatory assay method conforms to the criteria set forth in paragraph (d) of this section.

(1) The petitioner shall supply the validating laboratories with the number and amount of dosed and control tissue samples requested by the Commissioner.

(2) The petitioner shall supply reagents, standards, supplies, and equipment not readily available to the validating laboratories, as requested by the Commissioner.

(g) The Commissioner will evaluate the data gathered from the study described in paragraph (f) of this section. The assay shall be approved if it meets the criteria set forth in paragraph (d) of this section in each of the three validating laboratories.

§ 500.92 Withdrawal periods.

(a) The withdrawal period shall be the time after cessation of administration of the sponsored compound necessary for the marker residue to deplete, with 99 percent assurance, to L_m in the target tissue. The time will be extended if necessary to be consistent with conditions of livestock management reasonably certain to be followed in practice. The petitioner shall submit studies of the marker residue's depletion from the target tissue of animals dosed according to the maximum level of use proposed in the petition. The validated regulatory assay must be used to collect these data.

(1) The petitioner shall submit a plot of the concentration of marker residues in target tissue as a function of time (depletion curve) including the 99 percent confidence limits on the observed values.

(2) All raw data and statistical analyses shall be submitted along with a referenced discussion of the results.

(3) Use of the sponsored compound shall be approved only if the available evidence demonstrates that the proposed conditions of use, including any withdrawal period, are reasonably certain to be followed in practice.

(b) When the marker residue is an endogenous compound, the withdrawal period shall be the time required after cessation of administration of the sponsored compound for the norm to be restored, with 99 percent assurance. The time will be extended if necessary, but not reduced, to be compatible with conditions of livestock management reasonably certain to be followed in practice. The validated regulatory assay must be used to collect data on the rate of restoration of the norm.

(1) The petitioner shall submit a series of curves that demonstrate the time required for restoration of the norm.

(2) All raw data and statistical analysis shall be submitted along with a referenced discussion of the results.

(3) Approval of the petition for the sponsored compound shall be granted only if the available evidence demonstrates that the proposed labeling is reasonably certain to be followed in practice.

§ 500.94 Publication of the approved regulatory assay.

The lowest level of reliable measurement (L_m), the complete regulatory assay for measuring the marker residue in the target tissue, and the analytical curve shall be published in the FEDERAL REGISTER, in accordance with the provisions of sections 409(c)(3)(A), 512 (d)(1)(H) and (i), and 706(b)(5)(B) of the act. For an endogenous marker residue, the norm shall also be published.

§ 500.96 Waiver of requirements.

The Commissioner, in response to a petitioner or on his own initiative, may waive, in whole or in part, any of the foregoing requirements for the scientific evaluation of sponsored compounds that have the potential to contaminate human food with residues whose consumption could engender a human risk of carcinogenesis. A petition for such waiver may be filed by any person who would be adversely affected by the application of the requirements to a particular compound. The petition shall explain and document why some or all of the requirements are not reasonably applicable to the compound, and describe the alternative procedures that have been, or could be, followed to assure that use of the compound will not contaminate human food with residues whose consumption could engender a human risk of carcinogenesis and that an assay method exists that satisfies the requirements of § 500.90(d) (1) through (4) and that is capable of measuring any such residues that might occur when the compound was improperly used. The petition shall set forth clearly the reasons why the alternative procedures will provide the basis for concluding that approval of the compound satisfies the requirements of the anticancer provisions of the act. If the Commissioner determines on his own initiative that waiver of any of the foregoing requirements is appropriate, he shall so state and set forth the basis for that determination in the regulation approving marketing of the sponsored compound.

§ 500.98 Implementation.

(a) The requirements of this subpart shall apply to all new animal drug applications, feed additive petitions, and appropriate color additive petitions (i.e., all compounds intended for use in food-producing animals) submitted to the Food and Drug Administration subsequent to the effective date of the subpart, including appropriate supplemental applications, and to all such applications or petitions on file with the agency on the effective date of the subpart except to the extent that the Commissioner determines that consumer protection can be adequately assured by imposing such requirements in accordance with the provisions of paragraph (b) of this section.

(b) The provisions of this subpart shall also apply to the following compounds already approved:

01171

(1) Those compounds that the Commissioner determines, on the basis of available, reliable information, have been shown to induce cancer when ingested by man or animals.

(2) Those compounds that the Commissioner determines may induce cancer when ingested by man or animals, i.e., suspect carcinogens.

(3) Any compound for which the Commissioner concludes sufficient information has not been provided to determine whether that compound is appropriately regulated under the general food safety provisions of the act or under the anticancer provisions of the act.

(c) Any compound already approved to which the Commissioner determines the anticancer provisions of the act are applicable, or for which additional data are required for such a determination, will be the subject of a notice published in the FEDERAL REGISTER or a letter issued pursuant to section 512(1) of the Act establishing the time within which the requirements of this subpart must be satisfied.

(1) Notices already published in the FEDERAL REGISTER and letters already sent by the Food and Drug Administration requiring additional studies or submission of an improved regulatory assay shall remain in effect, and the provisions of this subpart shall be used in determining compliance with the requirements of the act identified in those notices and letters.

(2) The Commissioner will proceed to withdraw approval of any compound on the basis of data or information indicating a health hazard or in response to any failure to undertake studies necessary to comply with the provisions of this subpart.

PART 514—NEW ANIMAL DRUG APPLICATIONS

3. In Part 514, by amending § 514.111, by adding a new paragraph (a)(10) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(10) Such drug fails to satisfy the requirements imposed by Subpart E of Part 500 of this chapter.

* * * * *

PART 571—FOOD ADDITIVE PETITIONS

4. In Part 571, by adding a new § 571.115, to read as follows:

§ 571.115 Application of the anticancer cause of section 409].

Food additives intended for use as an ingredient in food for animals that are raised for food production must satisfy the requirements imposed by Subpart E of Part 500 of this chapter.

Effective date. These regulations shall be effective March 23, 1977. Interested persons may, on or before April 25, 1977 submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments, in quadruplicate and identified with the Hearing Clerk docket number found in brackets on the heading of this document, regarding these regulations. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any changes in this order justified by such comments will be the subject of a further order amending the specific regulations involved.

(Secs. 402, 403, 409, 512, 701(a), 706, 52 Stat. 1046-1048 as amended, 1055, 72 Stat. 1785-1788 as amended, 74 Stat. 399-403, 82 Stat. 343-351 (21 U.S.C. 342, 343, 348, 360b, 371(a), 376).)

NOTE.—Incorporation by reference provisions approved by the Director of the Office of the Federal Register on July 11, 1973, and February 15, 1977, and on file in the library of that office.

Dated: February 14, 1977.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.77-5266 Filed 2-16-77;8:45 am]

01172

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 70, 500, 514, 571]

[Docket No. 77N-0026]

CHEMICAL COMPOUNDS IN FOOD-PRODUCING ANIMALS

Criteria and Procedures for Evaluating Assays for Carcinogenic Residues

AGENCY: Food and Drug Administration.

ACTION: Proposal.

SUMMARY: The Food and Drug Administration (FDA) is proposing to establish procedures and minimum criteria to ensure the absence of cancer-causing residues in edible products of food-producing animals to which drugs, food additives, or color additives have been administered. This is a reproposal of regulations revoked in accordance with a court order.

DATES: Comments by July 18, 1979: Notices of participation for the public hearing by May 4, 1979. Public hearing before the Commissioner June 4, 1979.

ADDRESSES: Comments and notices of participation are to be submitted to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR INFORMATION ON THIS PROPOSAL, CONTACT:

Robert J. Condon, Bureau of Veterinary Medicine (HFV-105), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1580.

FOR FURTHER INFORMATION ON THE HEARING BEFORE THE COMMISSIONER CONTACT:

Constantine Zervos, Director, Scientific Liaison and Intelligence Staff (HFY-31), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4490.

SUPPLEMENTARY INFORMATION: These proposed regulations would provide an operational definition of the no-residue requirement of the so-called "DES proviso" to the anticancer clauses, sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B), of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(c)(3)(A), 360(d)(1)(H), and 376(b)(5)(B)). The regulations also propose to establish criteria for accepting assays and procedures for establishing suitable postadministration withdrawal periods to prevent the occurrence of carcinogenic residues in edible animal products.

Prior to July 19, 1973, FDA had applied the DES proviso on a case-by-case basis, without published criteria. However, the Commissioner of Food and Drugs concluded that it was appropriate to establish criteria and procedures for their application through rulemaking to permit public discussion of the scientific, legal, and policy issues involved. Accordingly, the Commissioner proposed a set of regulations, in the FEDERAL REGISTER of July 19, 1973 (38 FR 19226), and afforded 60 days for public comment.

The numerous comments received were submitted by scientists affiliated with consumer groups, universities, scientific societies, State and Federal agencies, trade associations, and affected manufacturers; some were from nonaffiliated individuals. Many comments revealed a sharp divergence of opinion concerning FDA's interpretation of the proviso to the anticancer clauses of the act.

The Commissioner promulgated the final regulations in the FEDERAL REGISTER of February 22, 1977 (42 FR 10412), but solicited comments on four specific issues: (1) The acceptable level of risk, (2) comparative metabolism, (3) regulation of endogenous compounds, and (4) methods of determining an assay's lowest limit of reliable measureent. On March 23 and 24, 1977, the Animal Health Institute (AHI) and three other groups petitioned the Commissioner to stay the effective date of the regulations and to then revoke them. The Commissioner denied these petitions on April 27. In response to a separate request by AHI, however, the Commissioner extended the comment period to July 25, 1977 (42 FR 24254).

On May 12, AHI filed a complaint in the United States District Court for the District of Columbia alleging that the regulations were unlawful: (1) because they broadened the scope of the Delaney, i.e., anticancer, clause of the act to include substance that have not been determined to be carcinogenic, and (2) because they foreclosed marketing of a compound unless there exists an assay of sufficient "sensetivity" to detect residues of the compound at "theoretically" safe levels determined by the regulations. Also, AHI alleged that the regulations were impractical and embodied novel on highly suspect technical principles that would impose enormous financial and environmental costs on the animal health industry. Finally, it alleged that the final regulations violated the Administrative Procedure Act (5 U.S.C. 551 note) because they departed from and radically changed the proposed regulations and were not republished for comment.

Based on AHI's affidavits contending that the statistical procedure for extrapolation of animal data adopted in the final order was significantly different from and more complex than that proposed, and perhaps improperly interpreted, the court remanded the case to the agency for further consideration. The court also required the agency to assess the question raised by AHI about the technical feasibility of the regulations, and it suggesed that the Commissioner repropose the regulations (*Animal Health Institute* v. *Food and Drug Administration*, Civil No. 77—806 (D.D.C. Feb. 8, 1978)). In accordance with the court's order, the Commissioner revoked the regulations on May 26, 1978 (43 FR 22675) and is now reproposing all the regulations for public comment. In this proposal, the Commissioner has evaluated and responded to AHI's allegations, the court's questions, the citizen petitions to revoke the regulations, and all comments filed on the final order. (For the sake of clarity, the final order is hereafter designated the "February notice" or the "1977 notice".)

Since the July 1973 proposal, the Commissioner has used the risk assessment element of the regulations as the prototype for segments of the agency's anticancer policy. Before attempting to build a uniform procedure for regulating all chemicals in the food supply, the Commissioner has adopted where appropriate, the best elements of the emerging scientific and regulatory procedures of risk assessment, metabolism studies, in vitro mutagenesis tests, etc., for regulating residues in food derived from food-producing animals.

The Commissioner selected this class of compounds as the test model because FDA has premarket approval authority over the chemicals intentionally used in these animals, and the DES proviso to the Delaney clause has made regulation of these compounds one of the agency's most difficult tasks.

Based on experience with the principles outlined in the proposal, gained through several years of regulating these chemicals on a case-by-case basis, the Commissioner believes that they have potential applicability for regulating all compounds covered by the act. Moreover, due to the extensive interest in the issues, the Commissioner now believes that the time is ripe for formulating a comprehensive approach for regulating all chemical carcinogens. Expanding the use of the principles set out in these regulations into other areas regulated by the agency seems desirable from the perspectives of science and public health protection, but the results of their ex-

01173

panded use, e.g., cost, cannot now be calculated.

Because an error in selecting the basic principles could lead to a future tragedy, the principles adopted at this time must be reasonable and must not underestimate the potential risks associated with the use of chemicals. Accordingly, the Commissioner is proposing to adopt principles that some may consider too "conservative." The term "conservative," however, is relative. Further, although the principles form an integrated scheme of regulation, individual segments can be severed and replaced.

For all the foregoing reasons, the Commissioner has determined that, in addition to the 120-day comment period for filing written comments, an informal public hearing should be held in accordance with Part 15 (21 CFR Part 15). The informal public hearing will provide an open forum for the presentation of information, views, and discussions on all aspects of the proposal. Because the general principles articulated in the regulations have widespread potential use, the Commissioner asks that the witnesses focus on the principles that form the basis of the regulations, in addition to the issue of the technical feasibility of the required analytical technology. In particular, the Commissioner requests discussion of the following:

1. Threshold assessment procedures.
2. Criteria for selecting residues for chronic toxicity testing.
3. The types of investigations necessary to study how chemicals are metabolized, and the role of these studies in assessing the parent compound's safety.
4. The use of comparative metabolism studies for selecting the laboratory animal species to be used as surrogates for man in chronic toxicity testing.
5. The utility of short-term in vitro mutagenesis tests in assessing the safety of a compound.
6. Mathematical risk estimation procedures, including (a) methods of assessing risks within a species and (b) methods of cross-species extrapolation.
7. Procedures for combining data from the same or different carcinogenesis bioassays.
8. The regulation of endogenous substances.
9. The acceptable level of risk.

In preparing final regulations, the Commissioner will consider the administrative record of this hearing along with all other written comments received during the comment period specified in this proposal and on the transcript of the Part 15 hearing.

The hearing will be held on June 4, 1979, starting at 9 a.m. in the Washington, DC area at a place to be announced later.

A written notice of participation must be filed in accordance with § 12.45 (21 CFR 12.45) with the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, not later than May 4, 1979. The envelope containing the notice of participation, and the notice of participation itself, should be prominently marked "SOM Hearing." The notice of participation must also contain Hearing Clerk Docket No. 77N-0026, the name, address, and telephone number of the person desiring to make a statement, along with any business affiliation, the text of the presentation, and the approximate length of time requested for the presentation. The Commissioner is requiring submission of the text of all presentations before the hearing to promote a comprehensive discussion of the issues, but the Commissioner recognizes that some revisions in the text before the hearing may be necessary. A schedule for the hearing will be mailed to each person who files a notice of participation; the schedule will also be available from the FDA Hearing Clerk. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations.

If the responses to this notice of hearing are so numerous that insufficient time is available to accommodate the full amount of time requested in the notices of participation received, the Commissioner will allocate the available time among the persons making the oral presentation to be used as they wish. Final versions of written statements (preferably four copies) should be presented to the presiding officer on the day of the hearing or submitted to the Hearing Clerk by June 19, 1979 for inclusion in the administrative record.

The plenary hearing will be open to the public, and any interested person who has filed a written notice of participation may be heard concerning matters raised in the written statement which are relevant to the issues under consideration.

Additional comments from interested persons may be submitted during the period following the hearing until the end of the comment period.

I. Introduction

A. Statutory Background

1. Food Additives Amendment of 1958

Section 409 of the Federal Food, Drug, and Cosmetic Act (Food Additives Amendment of 1958, Pub. L. 85-929) establishes criteria and prescribes procedures for FDA's premarket review and approval of food additives that have been shown to be safe. Section 409 was enacted to protect consumers by requiring substances that are intentionally added to food, or may reasonably be expected to become components or otherwise affect the characteristics of food, to be shown to be safe through rigorous scientific testing procedures. As the legislative history of the amendment demonstrates, one primary function was to protect the health of consumers by requiring manufacturers of food additives and food processors to test any potentially unsafe substances that are added to food in accordance with principles deemed appropriate by qualified scientists (Ref. 1).

Before the amendment, FDA's authority for ensuring the safety of food additives was limited to sections 402(a)(1) and 402(a)(2)(A) as enacted in 1938. Under these sections the agency must show that an intentionally added food substance may be injurious to health. Thus, the agency has to test the poisonous or deleterious substance before taking action. Therefore, the amendment shifted the burden of both testing and proving safety to the proponent of the additive.

When the Committee on Interstate and Foreign Commerce reported the bill to the full House of Representatives, the bill did not contain an anticancer clause, but it did contain a section requiring the premarketing testing of food additives to demonstrate safety. That section is now known as the general safety provision (section 409(c)(3)(A)). After the bill was reported out, Congressman Delaney suggested the addition of the anticancer proviso to the bill, and the following proviso was added to the bill as a Committee amendment on August 13, 1958:

> * * * *Provided*, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *.

Reportedly to assure enactment of the legislation, the Committee and the Department of Health, Education, and Welfare (HEW) agreed to the amendment, but in a letter to the Chairman of the Committee, then Assistant Secretary Elliot L. Richardson noted that the amendment did not change the meaning of the bill. Moreover, the letter also illustrates the interaction between the general safety and anticancer provisions of the bill and the broad scope that the Delaney anticancer clause is to be given. It makes clear that the anticancer clause is a corollary of the general safety clause; and that compounds, even when subject to the anticancer clause, are also subject to the general safety clause:

> This Department is in complete accord with the intent of these suggestions—that

no substance should be sanctioned for use in food that might produce cancer in man. H.R. 13254, as approved by your committee, will accomplish this intent, since it specifically instructs the Secretary not to issue a regulation permitting the use of an additive in food if a fair evaluation of the data before the Secretary fails to establish that the proposed use of the additive will be safe. The scientific tests that are adequate to establish the safety of an additive will give information about the tendency of an additive to produce cancer when it is present in food. Any indication that the additive may thus be carcinogenic would, under the terms of the bill, restrain the Secretary from approving the proposed use of the additive unless and until further testing shows to the point of reasonable certainty that the additive would not produce cancer and thus would be safe under the proposed conditions of use. This would afford good, strong public health protection (Ref. 2).

As enacted in 1958, the anticancer (or so-called Delaney) clause of section 409 flatly proscribed the approval of any additive if after "a fair evaluation of the data before the Secretary" the additive "is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *." As applied to additives added directly to human food, this language has remained unchanged, although hotly debated. Accordingly, as a legal matter, section 409 precludes a finding by FDA that a direct food additive that has been shown, by ingestion or other appropriate studies, to cause cancer in laboratory animals (or, of course, in man) can be safely added to food, in any amount, for any purpose.

2. Color Additive Amendments of 1960

The Color Additive Amendments of 1960 (Pub. L. 86-618) added a provision to the basic act for colors that is directly analogous to the food additives provision. Petitioners for color additive regulations must demonstrate by rigorous testing the safety of these additives before they can be approved by FDA for addition to food, drugs, or cosmetics. In addition, the amendments added another anticancer clause to the act.

The legislative history of the Color Additive Amendments of 1960 describes the congressional and executive (HEW) concern about the potential carcinogenicity of these color additives; nevertheless, the Secretary of HEW again explained that an express anticancer clause was unnecessary to prevent approval of carcinogenic or potentially carcinogenic color additives because it did not provide any public protection that is not already provided by the general safety clause (Ref. 3).

3. Drug Amendments of 1962

In 1962, Congress culminated several years of hearings on the drug industry by enacting the Drug Amendments of 1962 (Pub. L. 87-781); the infamous thalidomide incident provided the impetus for the bill's passage. The drug amendments brought about a comprehensive revision in the regulation of new drugs, which at the time included both human and animal drugs. The drug legislation also amended the anticancer clauses to rectify what Congress perceived as the inequity associated with the prior sanctioned use of diethylstilbestrol (DES) in animal feed. Under the Food Additives Amendment of 1958, certain DES uses in animals were prior sanctioned because they were covered by an effective New Drug Application (NDA). Thus, continued use in accordance with the prior sanction was appropriate until that use was cancelled (the NDA revoked), but no new uses in food or food-producing animals were approvable due to the Delaney clause (Refs. 4 and 5).

The act requires that compounds administered to animals as food additives, color additives, or animal drugs be shown to be safe for use. As defined in section 201(u) of the act (21 U.S.C. 321(u)), the term "safe" clearly embraces the health of man, as well as the health of the animals to which the compounds are given. Thus, in evaluating the safety of compounds to be administered to animals raised or maintained for production of food for man, such as cattle, swine, and poultry, Congress has from the beginning recognized that consideration must be given to the safety of possible residues of the compounds in the products of animals that become food for man, i.e., meat, milk, and eggs.

Before 1962, the anticancer clauses in sections 409 and 706 did not distinguish between compounds added directly to human food and compounds that might indirectly enter human food through administration, as feed additives or drugs, to food-producing animals. The act was interpreted as forbidding FDA to approve the use of a carcinogenic animal drug whether or not the compounds might leave any residues in the edible tissues of the animal.

Modification of the effect of the anticancer clause of section 409 had first been suggested during congressional consideration of the Color Addition Amendments of 1960. In May 1960, the then Secretary of Health, Education, and Welfare had urged Congress to modify the act, explaining:

> There is * * * one respect to which the anticancer proviso has proved to be needlessly stringent as applied to the use of additives in animal feed. For example, in the case of various animals raised for food production, certain drugs are used in animal feed which will leave no residue in the animal after slaughter or in any food product (such as milk or eggs) obtained from the living animal, and which are therefore perfectly safe for man. If this is demonstrated with respect to any particular additive intended for animal feed, and the additive will not adversely affect the animal itself during its expected or intended life cycle, we can see no reason for not permitting such a use of an additive which could be highly useful and beneficial in the raising of animals for food. * * *
>
> We therefore have included in the enclosed draft bill an amendment to permit use of an additive in animal feed under the above-mentioned conditions.
>
> * * * * *
>
> Under the amendment, the assay methods applicable in determining whether there will be a residue shall be those prescribed or approved by us by regulations. This will give reasonable certainty in that regard, although, of course, such regulations may from time to time be changed as new scientific developments demonstrate a need for change. It should be clearly understood that the industry still would have the responsibility of developing adequate analytical methods for detecting residues and furnishing them to the Government with a petition for approval of an additive (Ref. 3).

The amendments proposed by the Department had not been included in the color additive legislation. During the following 2 years, however, concern had been continuing about application of the anticancer clause in section 409. As a result, legislation similar to that earlier recommended by HEW was introduced in 1962. The House Committee on Interstate and Foreign Commerce ultimately included modifications of the anticancer clause in its report on the Drug Amendments of 1962, with the following explanation:

> The committee amended the anticancer clause of the food additives amendment and the color additive amendment of the Federal Food, Drug, and Cosmetic Act by making this clause inapplicable to chemicals such as veterinary drugs when used in feed for food-producing animals if the Secretary finds (1) that under the conditions of use and feeding specified in the proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (2) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations) in any edible portion of the animal after slaughter or in any food such as milk or eggs yielded by or derived from the living animal (Ref. 4).

Representative Leonor K. Sullivan objected to the proviso in the floor debate on the amendments and proposed a separate amendment to delete the proviso from the bill because "they (the provisos to the Delaney clauses) weaken instead of strengthen consumer protection." She reminded the House that DES had been regarded as safe for use in poultry at one

01175

time because no residue was found in the meat; later, that use had to be terminated when DES residues were found as a result of improved testing methods. But her amendment was defeated principally on the argument that, if DES were available for manufacture by those who obtained approvals before 1958, i.e., the prior-sanctioned uses, it should be made available for manufacture by everyone (Ref. 6).

The Senate accepted the modifications of the anticancer clauses in conference while preserving, as Senator Hubert Humphrey noted, the full vigor of consumer protection afforded by Delaney clause (Ref. 7). These modifications have come to be known as "the DES proviso."

4. Animal Drug Amendments of 1968

The animal feed industry experienced an era of unprecedented growth and innovation beginning in the 1950's. That industry and the animal drug industry began an effort in the mid-1960's to consolidate the various provisions of the Federal Food, Drug, and Cosmetic Act governing the premarketing approval of drugs intended for use in animals, i.e., sections 409, 505, 507 (21 U.S.C. 348, 355, and 357) which culminated in the enactment of the Animal Drug Amendments of 1968 (Pub. L. 90-399). Neither the committee reports on the bill nor the floor debates raised the issue of the Delaney clause. Consequently, the Animal Drug Amendments of 1968 passed without controversy and added, under section 512(d)(i)(H) of the act, the following anticancer clause and proviso:

(H) such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h)), in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals, * * *.

Again, the legislative history indicates that the legislation in no way weakens FDA's authority to regulate new animal drugs (Ref. 8).

B. STATUTORY INTERPRETATION

The enactment in 1962 of the so-called DES proviso to the Delaney clause has been a source of continuing controversy. There is no unanimity on the proper interpretation of the proviso; and the legislative history of the proviso, summarized above, does not lay to rest all doubts.

Two interpretations of the proviso are, in theory, possible. The first interpretation, which in the Commissioner's judgment is the less probable, is that Congress intended to allow FDA to approve the use of a carcinogenic compound in food-producing animals only if the agency could be absolutely positive that no traces whatever—no matter how small—would remain in edible tissues.

This interpretation presents several difficulties, all stemming from the fact that any introduction of a compound, whether or not carcinogenic, is likely to leave in edible tissues minute residues, which are below the level of detection of any known or likely to be developed method of analysis, i.e., assay. It is a fundamental fact of analytical science that for every assay developed to measure the concentration of a chemical compound in a medium (in this case, a residue in an edible tissue), there is some lowest concentration or level of the compound below which the assay will not yield an interpretable result (Ref. 9). If, for example, an assay measures a particular compound in muscle tissue, i.e., an edible tissue, and the assay has been shown to have a lowest limit of measurement of 1 part per billion (1 ppb—1 part compound in 1 billion parts tissue on a weight basis, such as 1 nanogram of compound per 1 gram of tissue), examination of muscle tissue using this assay will reveal that the compound is present only if its concentration in muscle tissue is 1 ppb or higher. If the compound is present in the tissue at a level below 1 ppb, use of the assay will yield no interpretable result. Thus, the assay connot distinguish between muscle tissues containing the compound at levels below 1 ppb and muscle tissues from which the compound is absent in the absolute sense of the term.

Although different assays may have different lowest limits of measurement, all assays are subject to the same type of limitation. Thus, when a tissue is examined with an assay having a lowest limit of measurement of 1 ppb and no interpretable response is observed, the analyst can conclude only that the compound under analysis is not present at a level of 1 ppb or above. It can never be concluded that the compound is "not present" in the absolute sense. It is thus impossible to determine the conditions under which edible tissues derived from food-producing animals that have received a carcinogen will contain no residue if the phrase "no residue" is to be interpreted literally. Accordingly, this first possible interpretation of the DES proviso would not permit approving any known carcinogenic animal drug because the Commissioner could never find that no trace whatever would remain in the edible tissues of the animals to which the compound was administered.

This interpretation would thus render the DES proviso a "Catch-22." The proviso would permit the Commissioner to approve carcinogenic drugs for animals only when certain that no residues whatever would remain, but since the Commissioner could conclude only that some trace might well remain, no such drug could ever be approved.

Nevertheless, one comment on the February notice contended that Congress did indeed intend that the no-residue provision be a flat prohibition on any molecules of a carcinogen in food. The comment further argued that Congress did not understand fully the scientific ramifications of its action when it amended the pristine Delaney clause.

As the Commissioner noted in the February notice, the "absolutely no molecules" interpretation seems, at the very least, an improbable interpretation of an amendment enacted by Congress precisely because it wanted to relieve animal drugs from the rigid strictures of the anticancer clauses. Moreover, any interpretation of a statutory provision that would render it totally inoperative should be rejected unless considerations of overwhelming persuasiveness require that interpretation. No such considerations have been advanced in support of the "absolutely no molecules" interpretation of the DES proviso.

Furthermore, this interpretation is difficult to reconcile with the language of the DES proviso itself. It specifies that "no residue" may be "found * * * by methods of examination prescribed or approved by the Secretary * * * in any edible portion of such animals * * *." This language conspicuously avoids such words as "occur" or "remain," and instead, by use of the word "found" emphasizes detectability. Moreover, the same proviso refers to "conditions of use * * * reasonably certain to be followed in practice", suggesting a congressional recognition that some occurrences of these residues (i.e., resulting from unforeseeable misuse) might not require withdrawal of approval of a compound even if they were detected.

A second, and in the Commissioner's view more plausible, interpretation of the DES proviso accepts the words of the amendment and focuses on the previously quoted language, "no residue of such drug will be found * * * by methods of examination prescribed or approved by the Secretary by regulations * * *." Under this interpretation, a sponsored compound that is carcinogenic may be approved for use in ani-

01176

mals if examination of edible tissues by an assay approved by FDA reveals no residues. This interpretation also appears implicit in the limited case law addressing the issue (*Hess & Clark, Division of Rhodia, Inc.* v. *FDA*, 495 F.2d 975 (D.C. Cir. 1974), *Chemetron Corp.* v. *United States DHEW*, 495 F.2d 995 (D.C. Cir. 1974), and *AHI* v. *FDA*, *supra*).

This second interpretation is in essence the one that FDA has followed since the passage of the DES proviso. The agency has approved carcinogenic compounds for use in animal feed or as animal drugs on the basis of assays capable of measuring prescribed levels of residues.

The court in *AHI* v. *FDA* found lacking the agency's previous attempt to define and explain, as a binding rule, the criteria and procedures for evaluating assays for carcinogenic residues in edible products of animals. The court held that FDA had failed to provide adequate public notice. One purpose of this document is to correct that defect.

The Commissioner believes that the criteria to be applied in evaluating assays for carcinogenic residues in the edible tissue of food-producing animals must further the congressional intent to minimize public exposure to carcinogens, without nullifying the decision reflected in the DES proviso, as the first interpretation of the proviso would do. As explained more fully below, the criteria set forth in these regulations for evaluating assays for carcinogenic residues are minimum requirements. They are designed to identify assays that are (1) reliable and practical for use by a regulatory agency and (2) capable of measuring residues at levels that have been determined, on the basis of animal toxicity tests, to present no significant increase in human risk of cancer. An assay that does not meet both criteria cannot be approved. The Commissioner recognizes that, for some compounds currently in use, no reliable and practical assay capable of sufficiently low limits of measurement now exists and that approval of their continued use must therefore be reexamined.

Arguing that the Commissioner has incorrectly interpreted the Delaney clause, AHI contends that it is a precise statutory provision that must be construed very narrowly. Therefore, AHI charges that the Commissioner's interpretation has unduly, and illegally, broadened the scope of the anticancer clause. AHI contends that FDA must prove that a compound is a carcinogen before the petitioner for the compound's use is required to comply with any provision of the proposed regulations. Ostensibly, AHI argues that FDA must prove that the sponsored compound is a carcinogen before a petitioner is required to submit either comprehensive data from long-term animal studies (the fundamental information for assessing a compound's carcinogenicity), or certain data regarding the residues in food to which man will be exposed if the compound is approved. Also, AHI argues that FDA cannot prevent a sponsor from marketing a compound when any assay for a carcinogen is available, even if the assay fails to exhibit a lowest limit of reliable measurement required by the data and extrapolation procedure proposed in the regulations. Citing *Hess & Clark, Division of Rhodia, Inc.* v. *FDA*, AHI further contends that the Delaney clause imposes upon FDA a standard corresponding to the level of technology at the time the application for the compound (new animal drug application (NADA) or food additive petition) is approved. Moreover, AHI argues that the modified Mantel-Bryan procedure for statistically assessing the risk of chemical carcinogenesis, which was included in the February notice, is a theoretical procedure that would require petitioners to develop assays capable of measuring residues of compounds at levels that are far too conservative and that are technically and economically infeasible. The court in *AHI* v. *FDA* requested FDA to consider AHI's arguments on technical and economic feasibility.

AHI's argument concerning the burden of proof on the issue of carcinogenicity might have merit if the Delaney clauses stood alone and were applied in isolation from the other provisions of the FFDC Act. However, ever since their enactment, the anticancer clauses have been regarded as a particularization of the general safety sections of the act, to which they attach as provisos; and they have been applied in conjunction with the general safety provisions. They do not expand the scope of these sections. Under these general safety provisions, a compound cannot be approved unless it is shown to be safe and in every case the petitioner has the burden of showing safety. Section 409(c)(3)(A) prohibits approval of a food additive if "the data before the Secretary * * * fails to establish that the proposed use of the food additive * * * will be safe * * *." Section 706(b)(4) prohibits the Secretary from approving a color additive "unless the data before him establish that such use * * * will be safe * * *." Section 512(d)(1)B) requires the Secretary to deny approval of a new animal drug if "the results [of tests submitted to the Secretary] show that such drug is unsafe for use under [the conditions prescribed, recommended, or suggested in the proposal labeling thereof] * * * or do not show that such drug is safe * * *." These sections of the act do not impose on FDA any burden to prove that a substance is unsafe. Rather, they impose on the petitioner for approval the burden of showing that, under the proposed conditions of use, the compound is safe.

"Safe" means safe in all respects—including safe from carcinogenicity. Thus, AHI's argument that the burden is on FDA to show carcinogenicity rather than on the sponsor to show noncarcinogenicity is contrary to the clear language of the act. It would impose on FDA two burdens that Congress manifestly intended to impose on petitioners for approval of substances under the act—the burden of testing for safety and the burden of proof on the issue of safety. The Delaney clauses clarify and emphasize the congressional intent to protect the public from carcinogenic risks; AHI would transform them into clauses that reduce the protection from carcinogenic risks already provided by the general safety provisions.

The general safety provisions of the act provide the context for the Delaney clauses. Under them the sponsor of a compound must submit adequate tests by all reasonably applicable methods to show that the sponsored compound will be safe when used. This showing, of course, requires not only toxicity testing but also an assay suitable for measuring the compound and substances formed in or on food as a result of its use. Only after the sponsor of a compound has conducted all the required tests and submitted the resulting data is FDA required to make any showing that the Delaney clause or the DES proviso is applicable or that the compound has not otherwise been shown to be safe.

Adoption of AHI's interpretation that FDA must prove that a compound is a carcinogen before the necessary data are submitted requires an illogical reading of the statute in light of its overall purpose and the legislative mandate surrounding it. Therefore, the Commissioner rejects AHI's scheme of regulating chemical carcinogens and potential carcinogens.

Scrutiny of the *Hess & Clark* decision shows that the court did not even consider the procedure that FDA used to designate requiremens for an assay under the DES proviso to the Delaney clause; rather, the court accepted as valid the agency's designation of an assay. To the extent that the procedures and criteria set forth in this notice for assessing assays differ from those used in evaluating the assay involved in *Hess & Clark*, they are being adopted by rulemaking in an area in which the agency has considerable expertise and discretion because the area involves protecting the public against cancer.

AHI's allegations that the regulations are technically and economically infeasible is an attempt to characterize the agency's actions as arbitrary and capricious. Several environmental statutes (e.g., Clean Air Act, Federal Water Pollution Control Act, Federal

01177

Insecticide, Fungicide, and Rodenticide Act) contain specific provisions requiring the Environmental Protection Agency (EPA) in certain instances to make elaborate cost/benefit calculations in setting safe levels of human exposure to chemicals in the environment. Also, these statutes provide that EPA protect the environment from contaminants by setting standards for the discharges permitted. EPA is authorized to establish two types of standards—health-based standards and technology-based standards. For certain health-based standards the Supreme Court has authorized that agency to require pollution reduction by methods that are neither economically nor technically feasible when the agency is not explicitly required to consider cost (*Union Electric Company v. EPA*, 427 U.S. 241 (1976)). The United States Court of Appeals for the District of Columbia Circuit has subsequently reached similar conclusions when interpreting analogous provisions of the Federal Water Pollution Control Act, concerning regulation of the discharge of toxaphene endrin, and polychlorinated biphenyls (PCB's) (see *Hercules, Inc., et al v. Environmental Protection Agency, No. 77-1248, (D.C. Cir. Nov. 3, 1978); Environmental Defense Fund, et al. v. Environmental Protection Agency*, No. 77-1091 (D.C. Cir. Nov. 3, 1978)).

The two possible exceptions not applicable here (establishment of tolerances for unavoidable contaminants under section 406 and for pesticides under section 408(h)), the Federal Food, Drug, and Cosmetic Act contains no provisions requiring the Commissioner to consider costs or technical feasibility in making any safety decision, including any decision involving cancer-causing chemicals. The distinction between the statutory provisions applicable to food additives, color additives, and animal drugs and those applicable to pesticides and unavoidable contaminant tolerances demonstrates Congress' decision to make costs and technical feasibility relevant to some public health matters but not to others. Nevertheless, in light of the court's remand order, the Commissioner recognized the agency's obligations to review this element of the proposal. Based on the act's legislative history, the case law, and the agency's public protection function, the Commissioner concludes that the procedures used to designate requirements for assays can be technology-forcing if necessary.

The Commissioner's interpretation recognizes the tension between the need to provide health protection and the costs of that protection, and it attempts to spur the private sector into technological change only when such change is necessary for protection of the public health. To do otherwise might force the public to accept an increased disease burden that it would unknowingly have to bear. The agency recognizes that the public health is not advanced by imposing requirements for what is neither economically nor technically possible. It also recognizes that public health regulation requires common sense, a sense of proportion, and awareness of economic and technical factors. In particular, the agency should not impose economic costs that are not justified by some reduction of risks to the public health. Nevertheless, the agency can properly require improvements in or developments beyond currently available technology when there is sufficient reason to believe that those improvements or developments are feasible and are needed to protect the public health. In enacting public health legislation, Congress intends that administrative agencies carry out their assigned missions with intelligence, good sense, and an awareness of the context and consequences of their actions; but unless it has expressly said so, there is no reason to think that it intended them to be in thrall to the technological or economic status quo.

In the immediate context, the statutory structure and language provide considerable guidance with respect to the issue of feasibility and costs. The language permitting the use of carcinogenic substances under certain circumstances is a proviso to a clause prohibiting the use of carcinogens, and that clause itself is a particularization of a provision requiring safety generally. It is clear that in enacting the DES proviso Congress intended to create no additional risk of human cancer beyond what would have existed in the absence of the DEX proviso. That is why Congress used the language "no residue * * * will be found." By enacting and twice re-enacting the Delaney clause, Congress made clear its willingness to ban entirely from the human food supply food additives, color additives, and animal drugs that present a carcinogenic risk to man. It enacted the DES proviso with the intent and expectation that the provision that "no residue * * * will be found" would sufficiently protect the human food supply from any significant cancer risk from food additives, color additives, and animal drugs. Thus, in enacting the DES proviso, Congress did not change in any way the policy of the Delaney clause to protect the human food supply from carcinogenic additives and animal drugs; it merely eliminated an application of the clause that it considered unnecessary to the complete achievement of that policy.

From this statutory structure and language, it is evident that any consideration of feasibility and costs is subsidiary to the overriding congressional purpose to permit no additional human cancer risk from food additives, color additives, or animal drugs. The Commissioner's discretion to establish "methods of examination" for detecting residues is to be exercised so as to carry out that congressional purpose. the factor that determines the acceptable level of measurment of an assay method is protection of the human food supply from carcinogenic risks. If, on the basis of toxicological considerations, the Commissioner determines that a certain level of assay measurement is necessary to prevent a significant human cancer risk from use of a carcinogenic substance in food animals, then a method having that level of measurement is necessary to carry out the congressional purpose. If no such method is feasible, or if it is too costly to develop or apply one, then the choice is between refusing to permit the use of the substance altogether and permitting its use despite the fact there is no method of examination that can prevent the use of the substance from presenting a significant human cancer risk. Under the general safety clause and the Delaney clause, that choice can be resolved in only one way: by refusing to permit the use of the substance.

During the last decade, FDA has been monitoring significant trends in the development of chemical, physical, and biochemical methods of analysis of trace toxicants in biological matrices, i.e., tissues, biological fluids, etc. In some cases the agency has examined the available methods, and the trends, of analysis of specific toxicants of public health concern (Ref. 10). In other cases the agency has prepared and submitted to Congress reports on the advancing frontiers of the analytical sciences (Refs. 11 and 12). One of the central findings of this continuing activity is the observation of what can properly be regarded as spectacular scientific progress in achieving ever-decreasing lowest limits of measurement. There is no reason to believe that this progress in analytical chemistry will stop or slacken in the foreseeable future.

Table I shows the trend of the increasing capacity of analytical chemistry to detect the measure the presence of chemicals. Depending on the substance or class of substances, this decrease in the lowest limits of measurement during the last 20 years ranges between two and five orders of magnitude. Table I also suggests that recognition of a public health problem associated with a toxicant accelerates the improvement of analytical methods needed to detect and measure it. In this connection it should be noted that accelerated rates of improvement in analytical methods have generally been the result of public health concerns diffused among the members of the scientific community at large. They have not usually been the result of the concerted effort of a sponsor or industry to gain approval for use of a substance of commercial value.

TABLE I.—*Trends in Analytical Chemistry Detection Techniques*

Compound and date	Detection technique	Limit of measurement	Relative specificity
DDT:			
1940's, 1950's	Colorimetric	10 ppm	Low.
1950's, 1960's	Paper chromatography	1 ppm	Moderate.
1970's	Gas chromatography	Few ppb	Do.
	Gas chromatography/mass spec	Few ppb	High.
Dioxins:			
1940's			
1950's, 1960's	Thin layer chromatography	Nots quant	Moderate.
1970's	Gas chromatography/mass spec	Less than .1 ppb	High.
Nitrosamines:			
1940's			
1950's, 1960's	Thin layer chromatography	10-20 ppb	Moderate.
1970's	Gas chromatography/mass spec	2 ppb	High.
Cortisone:			
1940's			
1950's, 1960's	Colorimetric	4 mg/ml	Low.
1970's	High press liquid chromatography	About 5 ng	Moderate.
Chlorpromazine:			
1940's, 1950's	Titrimetric	50-100 mcg	Low.
1960's, 1970's	chromatography	A few mcg	Low.
Hallucinogens (LSD, mescaline):			
1940's			
1950's			
1960's	Colorimetry	mcg/ml	Low.
	Gas chromatography, fluorescence	25 ng	Moderate.
1970's	NMR	Sub ng	High.
Reserpine:			
1940's			
1950's, 1960's	Colorimetry	Greater than 10 ppm	Low.
1970's	Fluorescence	About 5 mcg/ml	High.
Lead:			
1940's	Colorimetry	About 10 ppm	Low.
	Polarography	About 0.1 ppm	High.
1950's	do	do	Do.
1960's	Atomic absorption	About 1 ppm	Do.
1970's	do	do	Do.
Cadmium:			
1940's			
1950's, 1960's	Colorimetry	About 50 ppb	Medium.
1960's, 1970's	Atomic absorption	About 0.5 ppb	High.
Digitalis drug:			
1940's	Bioassay	LD_{50} 80 mg/kg	Low.
1950's	do	do	Do.
1960's	do	do	Do.
1970's	Radioimmunoassay	About 0.5 ppb	High.
Carbamates:			
1940's			
1950's, 1960's	Thin layer chromatography, gas chromatography.	50-100 ng	Moderate.
1970's	Gas chromatography	About 1 ng	High.
Organophosphates:			
1940's			
1950's			
1960's	Gas chromatography	About 40 pg	Moderate.
1970's	do	do	High.

Next, Table II shows the capability of some assays that are currently being used to measure trace contaminants in food. Although the assays have not been evaluated by all the specific criteria proposed by the regulation, they are useful regulatory tools; and the lowest limits of reliable measurement for these assays (which were principally developed by the government for monitoring purposes) illustrate the forefront of current analytical chemistry.

TABLE II.—*Some Assays for Trace Contaminants in Food That Reflect Current Analytical Capabilities*

Substance under assay	Food	Limit of measurement [1]	Detection and confirmatory techniques	Reference [2]
Cadmium, copper, and lead	Several types	5	Anodic stripping voltammetry [3].	Jones, et al. (1977).
N-Nitrosamines	Several types including meat.	10	Gas-liquid chromatography (GLC); mass spectrometry (MS).	Fazio, et al. (1971); Fine, et al. (1975).
Aflatoxins, B1, B2, G1, G12	Peanut butter	5.0 [4]	High pressure liquid chromatography; fluorescence detector.	Pansalkate and Scott (1977).
Benzo(a)pyrene	Smoked foods	3	Thin layer chromatography [5] (TLC) ultraviolet and fluorescence detection.	Howard, et al. (1966).
Aflatoxin M1	Milk	0.1	TLC-fluorescence detection [6] chemical derivation.	Official Methods of Analysis of the AOAC.
Aflatoxin B1, B2, G1, G2	Peanut butter	5.0	TLC-fluorescence detection [6].	Official Methods of Analysis of the AOAC.
	Corn		TLC chemical derivation	Official Methods of Analysis of the AOAC.
Aflatoxin B1	Eggs	0.1	TLC-flourescence detection; chemical derivation.	Neaheim, et al. (1978).
Arsenic, selenium, antimony, and tellurium.	Several foods	10 to 30	Atomic absorption; spectrometry; chemical derivation.	Florino, et al. (1976).

TABLE II.—*Some Assays for Trace Contaminants in Food That Reflect Current Analytical Capabilities*—Continued

Substance under assay	Food	Limit of measurement [1]	Detection and confirmatory techniques	Reference [2]
Several chlorinated pesticides	Several foods	30 to 50	GLC-2 different	Official Methods of Analysis of the AOAC.
Tetrachlorodibenzodioxin	Fat, milk, others.	.0001 to .010.	Chromatography resolution MS probe).	high (direct O'Keefe, et al. (1975); Hummell, P. A. (1977).

[1] Parts per billion.
[2] References available from: John Arnold, Industry Information (HFV-228), Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.
[3] Found reliable in interlaboratory validation study.
[4] Sum of all four compounds.

In view of these trends, the Commissioner has examined the general analytical requirements that these regulations will place on animal drug sponsors. Table III below shows the acceptable total level of residues in the diet for representative compounds believed to be carcinogens. These estimated acceptable total dietary levels are derived from bioassay data on the parent compounds alone. The lowest limits of reliable measurement for these compounds that would be required if the compounds were subject to the proposed regulation cannot be calculated in the absence of metabolism data in animals in which a sponsored compound is proposed or intended for use (target aminals). Nevertheless, the values do approximate the limits of measurement that would be required by the regulations and are therefore suitable for comparison with the current analytical capabilities that are shown in Tables I and II. It should be noted that for some compounds the lowest limit of reliable measurement derived from toxicity data may go beyond current analytical capabilities; that it may, however, reflects the technology-forcing aspects of the proposed regulation.

TABLE III.—*Estimated Acceptable Total Dietary Levels of Several Known or Suspected Carcinogens for a Lifetime Risk Level of 1 in 1 Million*

Compound	Reference [1]	Dose [2]
DDT	Tomatis, et al. (1972)	.4
Dimethylnitrosamine	Terracini, et al. (1967)	.06
Ethylene Thiourea	Graham, et al.	2.0
NTA	National Cancer Institute Clearinghouse on Carcinogenesis.	360.0
Vinyl chloride	Maltoni (1975)	6.7

[1] Available from John Arnold, Industry Information (HFV-226), Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.
[2] Calculated according to Hoel, et al. (1975) (Ref. 65). (In parts per billion.)

The Commissioner concludes that given the known trends in the development of improved analytical methodology the imposed requirements are attainable at the expense of reasonable effort.

The goal of regulating compounds that are to be used in food-producing animals is to ensure that none is permitted to yield residues in edible tissues at concentrations presenting a risk of carcinogenesis above an acceptable level. This acceptable level of maximum allowable risk (see section V. C. 8 in this preamble) is applied to all carcinogens; thus, equitable treatment of all such substances is afforded by these regulatory requirements. Different carcinogens will require different assay capabilities because of differences in carcinogenic potency. The regulations are designed to require that the lowest limit of measurement of an assay be commensurate with a compound's carcinogenic potency. Because it is not possible to specify the required limits of measurement for carcinogens in the absence of animal bioassay data, it is not possible to ensure in advance that all compounds for which approval is sought in the future will be able to be used in ways that satisfy the requirements of the regulations. It may be that some substances present health risks so great that there is no current technology available that can permit their safe use. In these instances the Delaney clause (including the proviso) requires that the Commissioner not relax health standards in order to approve such substances.

From the information described above, the Commissioner believes that analytical science can meet these regulatory requirements. The Commissioner is not aware of any data to the contrary. Based on this review, the Commissioner has concluded that compliance with the proposed regulations is feasible, although some technological innovation may be necessary.

Questions have arisen about the practicality, efficiency, and overall public protection afforded by automatically adopting new assays that reliably measure lower levels of residues is such assays becomes available after a sponsored compound has been approved for use. In the February notice the Commissioner suggested that this problem is largely theoretical once an assay meeting the minimum criteria is approved. The decision to approve an assay for a sponsored compound under these principles represents the agency's conclusion that the compound has been shown to meet all the statutory requirements of safety. Accordingly, once assay methods have been approved, new methods will not be required wthout new toxicological data showing that the lowest limit of reliable measurement of residues under these regulations is inappropriate.

It is true that these proposed regulations will permit the approval, for use in animals feed or for use as animal drugs, of carcinogenic compounds that are likely to leave residues below the lowest level of reliable measuremnt of any assay meeting all the criteria of the regulation. Indeed, as a result of Congress' enacting the DES proviso, the agency will not have any certainty that these residues, in amounts below the level of detectability, are not always present. This result makes sense in practical terms, however, for a regulatory agency cannot effectively control residues—of any compound—that are so small that they escape measurement by every available assay. In sum, the interpretation adopted in these proposed regulations is reconcilable with both the purpose and language of the DES proviso. This interpretation will further the congressional objective of minimizing public exposure to residues of carcinogenic compounds. It does not force technology beyond the point that needs to be reached to carry out the purpose of the Delaney clause and the general safety provisions. It does not impose infeasible requirements or costs except to the extent that they are necessary to carry out that purpose.

C. OVERVIEW OF THE REGULATIONS

The proviso to the anticancer clauses allows the approval of the use of carcinogens in food-producing animals if, under conditions of use "reasonably certain to be followed in practice," no residue is found by an assay prescribed or approved by the Secretary. To ensure public protection consistent with the anticancer and the general safety provisions of the act, the Commissioner must establish criteria for approving assays to include, among other things, an adequate lowest limit of measurement.

Accordingly, these proposed regulations would establish criteria for accepting assays used to measure residues of carcinogens in edible tissues of food-producing animals to which carcinogens have been administered. Such criteria cover assay attributes such as dependability, practicability, specificity, accuracy, and precision. Also, the regulations would establish a specific criterion for the lowest limit of reliable measurement that an assay must meet, as a minimum, before it can be approved by the agency for control of carcinogenic residues. This criterion for the required lowest limit of measurement of an assay derives from toxicological data obtained from carcinogenicity studies and from an operational definition of the no-residue standard of the act. Only if an assay meeting the above criteria is available would the Commissioner have a mechanism to discriminate be-

01180

tween tissue containing a residue and tissue containing no residue. Without such a monitoring mechanism, the Commissioner would have no way to detemine whether a carcinogenic drug or additive administered to a food-producing animal is being or even can be used in compliance with the act.

In these regulations the Commissioner proposes to establish a rigorous premarket testing process for sponsored compounds intended for use in food-producing animals. As proposed, all sponsored compounds must initially undergo a threshold assessment for carcinogenic potential. For those sponsored compounds having a carcinogenic potential, a procedure is prescribed to determine the minimally acceptable lowest limit of reliable measurement for a regulatory assay. Because this limit is determined on the basis of toxicity data, the Commissioner may conclude that an assay satisfying the requirements of the regulations is capable of demonstrating the absence in food of residues that present a risk of cancer to man. By thus particularizing the statutory requirements, the Commissioner proposes to establish the basis for accepting or rejecting compounds which the sponsor claims satisfy the no-residue standards.

1. *Fundamental questions.* For every drug of additive proposed for use in food-producing animals (the sponsored compound), the Commissioner is required by the act to determine whether that sponsored compound can be used in ways that are safe for the animals to which the compound will be administered (target animals) and whether food (meat, milk, and eggs) derived from such animals (edible tissues) will be safe for human consumption. The sponsor of the compound is therefore required to furnish the Commissioner the scientific and technical information necessary for that determination; the Commissioner in turn is required by the act to determine on the basis of all available data whether, in actual practice, the sponsored compound can be used in compliance with the law.

Although a petitioner proposing to use a carcinogenic compound in food-producing animals has a major obligation to develop a practical and reliable assay capable of discriminating tissues that contain residues from tissues free of such residues, as defined operationally, such an assay cannot be developed without certain scientific and technical information.

Specifically, for every sponsored compound, several questions must be answered before an assay can be developed or approval of the compound considered:

a. What is the chemical nature of the sponsored compound and how is it to be used?

b. Based on preliminary toxicological and biochemical information, does the compound have the potential to contaminate human food (edible tissues) with residues of carcinogenic concern?

c. If so, what is the chemical nature of the residues of the compound? In what tissues are they found? at what levels? and for what length of time?

d. Is the sponsored compound or any of the residues it produces in edible tissue carcinogenic in experimental animals or man?

e. If so, what level of residues can be operationally defined as satisfying the no-residue requirement of the act?

f. Can a reliable and practical assay be developed to measure the edible tissue residues at levels equal to or greater than those which operationally satisfy the no-residue requirement of the act?

g. At what time after exposure to the compound ceases do the edible tissues of exposed food-producing animals satisfy the no-residue requirement of the act, i.e., what is the necessary withdrawal time?

2. *Date collection process.* To answer the preceding questions, a petitioner must gather pertinent scientific information, the nature of which is particularized in this document. These proposed regulations would establish the procedure for gathering and evaluating the requisite scientific information. The process is stepwise and evolutionary because the need, as well as ability, to proceed to the next step of data collection depends upon the results obtained at each preceding step. If the evaluation of the data collected at each step indicates that questions on residues of carcinogenic concern remain, data collection must continue. If at some point in the data collection process it can be decided that the sponsored compound presents no human risk of carcinogenesis, the sponsored compound must be evaluated for any other health concerns under the general safety provisions of the act. In this case, the compound may be assigned a safe tolerance level in human food if the petitioner provides the data necessary to establish that the compound can be used safely.

These proposed regulations deal with carcinogenesis, which is a dominant concern in appraising the safety of any sponsored compound intended for use in food-producing animals. Nevertheless, each compound must also be evaluated for other potential adverse effects. Thus, for example, if the available information raises an issue as to the health of progeny, multigeneration studies of the sponsored compound and/or its residues must be codesigned and conducted as part of the process of collection and evaluation of data.

Under this proposal, if the Commissioner makes a threshold determination that a sponsored compound has the potential to contaminate food from food-producing animals with residues whose consumption would pose a human risk of carcinogenesis, the petitioner will be required to undertake the following six-step procedure for data collection and evaluation.

a. A metabolic study in the target animals designed to identify edible tissue residues of carcinogenic concern.

b. Metabolic studies of the sponsored compound in different species/strains of experimental animals designed to aid in selecting the test animal species to be used in chronic toxicity bioassays and in assessing the carcinogenicity of residues that cannot practicably be tested individually ("intractable residues").

c. Chronic toxicity testing to assess the carcinogenic potential of residues of the sponsored compound and to furnish data suitable for statistical treatment so that the no-residue requirement of the act can be applied and implemented.

d. A detailed metabolic study of the sponsored compound in target animals designed to identify both a residue and tissue that can serve as indicators ("marker residue" and "target tissue") to determine whether the no-residue requirement of the act is satisfied.

e. Development of a regulatory assay to measure the marker residue in the target tissue at and above the level established in step d.

f. Establishment of the premarketing withdrawal period required for the safe use of the sponsored compound.

Although the particular provisos to the anticancer clauses of the act, sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B), vary slightly in their language, they have a common purpose. Therefore, the Commissioner believes that the criteria for their implementation should be identical. To avoid needless repetition, the Commissioner has used the language of section 512 of the act in discussing specific generic issues because the primary impact of these proposed regulations would be on new animal drugs regulated under that statute. The criteria set forth in this proposal would, however, apply to all chemicals intended for use in food-producing animals, and the appropriate regulations would be amended to adopt these criteria by reference.

II. Threshold Assessment

In the 1973 notice of proposed rulemaking, the Commissioner proposed that carcinogenicity testing not be required for every sponsored compound. Rather, the Commissioner concluded that the necessity for such testing will be dictated by an evaluation of the ex-

01181

isting evidence from metabolic studies, toxicity testing, structural relationships of the sponsored compound and its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended method of use of the sponsored compound.

Comments of two types were received on this feature of the proposal. The first suggested that extensive studies should be conducted from every sponsored compound to determine whether it is a carcinogen. One comment insisted that extensive carcinogenesis testing for every sponsored compound is the only accurate indicator of carcinogenic potential. Several contended that the criteria proposed for use in the threshold assessment were too vague, and objected to the failure to explain how such criteria could be applied in practice. Many other comments agreed with the Commissioner's proposal that extensive carcinogencity testing should not be required for every sponsored compound. These comments recommended that the Commissioner review all available data on a sponsored compound before concluding that the stepwise testing procedure set forth in the proposals should be invoked. Comments of a similar nature were received on the 1977 notice. Furthermore, several comments asserted that the guidelines for the threshold assessment were not specific enough.

The Commissioner agrees that the guidelines for the threshold assessment were insufficiently specific, and the following discussion elaborates the agency's guidelines for conducting threshold assessments.

For every compound intended for use in food-producing animals, the fundamental question to be answered is: "What is the potential that the proposed use of the sponsored compound will contaminate the edible tissue of target animals with residues that engender a risk of cancer to humans?"

When a sponsor starts the process of obtaining approval for use of a compound, it provides to the agency information on matters such as the compound effectiveness and its proposed patterns of use. Often a sponsor will also provide preliminary physiological, metabolic, or toxicological data derived from its own studies or from the scientific literature. At this juncture, the Commissioner believes it necessary that a threshold assessment be made, based on the available data, on the need to proceed to the first of the six steps of data collection required by these proposed regulations. Because entry into the six steps of data collection requires that a petitioner undertake a series of complex and costly experimental studies, the Commissioner concludes that it is not reasonable to demand such studies on a sponsored compound if the preliminary data available justify the determination that public health can be protected without so proceeding.

For the sake of clarity, "the total residue of the sponsored compound" and "residue of toxicological concern" are defined in proposed § 500.83 as follows:

> "The total residue of a sponsored compound" means all compounds present in edible tissues of target animals that result from the use of the sponsored compound, including the sponsored compound, its metabolites, conversion products, and any other substances formed in or on food because of the sponsored compound's use. (The term "residue" means any single compound present among the total residue.)
>
> "Residue of toxicological concern" means the total residue minus any constituent residue shown to be safe.

A. GENERAL PRINCIPLES

The threshold assessment is based on the principle that the probability that the use of a sponsored compound will yield edible food animal tissue presenting a risk of human carcinogenesis from residue is the product of the following three factors:

(1) The probability of human exposure to residues that may cause cancer, given the proposed pattern of the sponsored compound's use (Factor 1—Use);

(2) The expected average level or concentration of residues of toxicological concern in the edible tissue of treated target animals under the proposed conditions of use, i.e., when the animals have the potential for marketing as food (Factor 2—Residues of toxicological concern); and

(3) The probable toxicological significance of the residues, based on an assessment of the chemical structure of the sponsored compound, its likely metabolites, and other information suitable for predicting toxicity (Factor 3—Potential toxicological significance).

The threshold assessment functions on the premise that all three of these factors must be considered to answer the fundamental safety question posed above. Under the agency's threshold assessment approach, numerical scores are assigned to the sponsored compound, and each of the three scoring factors contributes to the total score. The following paragraphs describe the scoring system and procedures that can be used to collect data that may lead to information yielding the most reliable scores. By consulting this guideline, sponsors of compounds can assess the status of the sponsored compounds for which they seek approval and may therefore provide relevant and useful preliminary data.

The scoring system uses a value of 1,000 to discriminate between those compounds that will be regulated solely according to the general food safety requirements of the act and those compounds that will, in addition, be subject to this proposed regulation. This system will provide uniformity to the threshold assessment of the risk to the public health from a sponsored compound's residues.

When the only preliminary information available is the proposed pattern of use (factor 1 above), the sponsored compounds will be subject to step 1 of the proposed regulations (§ 500.80(b)(1)(i)). Since without the necessary information FDA must make assumptions that require entry into step 1, petitioners have an incentive to gather pertinent information before approaching FDA.

This decision may be altered or confirmed by subsequent collection of data under these proposed regulations or under the other aspects of the general safety provisions of the act. For example, data collected to satisfy other concerns also covered in the general safety provisions may show that the compound is a potential carcinogen. In that case the compound will be evaluated under these proposed regulations. The obverse is also true.

B. THE SCORING SYSTEM

The total threshold assessment score for a sponsored compound is the product of the values for the three assessment factors.

1. *Factor 1—Use.* The use classification of sponsored compounds is divided into three categories, based on the frequency and extent of the target animal's treatment with the sponsored compound. The use factor is the probability that potentially consumable target animals will be treated with the sponsored compound. (See Table IV.) The values in Table IV represent ratios that approximate the likelihood of human exposure from the proposed use patterns in animals.

TABLE IV.—USE FACTOR ASSESSMENT

Frequency and scope of target animal treatment	Score
Administration to individual animals to prevent or treat disease	1
Administration on a herd-wide or flock basis for disease treatment or specific disease prevention (for problem herds or when outbreak of disease has occurred)	10
Administration on a herd-wide or flock basis for production improvement or general disease prevention (e.g., coccidiosis)	100

2. *Factor 2—Residues of toxicological concern.* For this scoring factor, the agency assigns the number equal to the concentration in parts per billion of the total residue of toxicological concern occurring in the edible tissue that is the most efficient accumulator of residues in the target animals at the earliest time the animals

01182

are expected to be marketable as food. Without total residue data, the sponsored compound will automatically be required to proceed to step 1 in proposed § 500.80(b)(1)(i).

Lacking information on the composition of the total residue in the edible tissues, the agency must assume that the total residue is of toxicological concern. The score value may be lowered if the sponsor gathers information on the composition of the total residue. For example, a sponsor may demonstrate that a portion of the total residue is a compound for which adequate studies have already been conducted to show that its presence as a residue is not of human health concern.

3. *Factor 3—Potential toxicological significance.* The values for scoring factor 3 reflect the agency's concern that the residues resulting from use of the sponsored compound are likely to cause cancer. The value will be obtained by taking into account available information concerning the potential toxicological activity of the residues themselves or of structurally related compounds, and compounds related by common physiological activity. The Commissioner recognizes that structure/activity relationships and the short-term biological tests discussed later have not been sufficiently developed to permit definitive predictions of carcinogenic activity (Refs. 13, 14, and 15). Nevertheless, the Commissioner believes that they can make a contribution to the threshold assessment.

In the following paragraphs, three sources of information on the basis of which the third factor is scored are discussed: (a) Structure/activity relations; (b) short-term screening tests for carcinogenic potential; and (c) other biological, physiological, and pharmacological data.

The possible values for scoring factor 3 are 1, 10, and 100. A score of 100 is assigned if there is evidence from any of the three sources of information that raises a suspicion that the residue is carcinogenic. A score of 10 is assigned if short-term screening tests for carcinogenic potential have not been conducted and there is no basis for suspecting carcinogenic activity based on the other sources of data.

A score of 1 is assigned when a battery of short-term screening tests for carcinogenic potential has been conducted, when the results show no reason to suspect carcinogenesis, and when there is no suspicion of a carcinogenic potential raised by the other information sources.

(a) Structure/activity assessment: FDA maintains a list of structural characteristics that can be used as a guide in initially determining when, based on structure alone, there may be concern about carcinogenic potential. The list includes all structural types for which one or more compounds have been shown to produce cancer in animals or man. Specific functional groups, e.g., aromatic nuclei, are included where there is evidence that these groups are the dominant influence in carcinogenic potential (Ref. 16).

Because new information is rapidly gathering in this area, the Commissioner expects the FDA list to be updated frequently and recognizes that this list is not exhaustive. An FDA committee on structure/activity relationships will provide an in-depth evaluation of substances with structural features found on the list before a final score is assigned.

(b) Screening tests for carcinogens: Evidence about the validity and utility of short-term in vitro tests as tools for regulating chemicals is growing rapidly. The Commissioner has concluded, however, that they cannot be used as the principal tool in assessing the safety of a compound. An appropriate battery of such tests can provide useful but not conclusive information about the safety of chemicals quickly, and at a reasonable cost. For these reasons, the Commissioner has included this section in the preamble as a guide to using these tests.

Currently, an appropriate battery of short-term tests includes both mammalian and nonmammalian test systems. The battery should test the ability of a sponsored compound to induce point mutations in two test systems that have been demonstrated to have a high correlation between detected mutagens and positive results in in vivo carcinogenesis bioassays. Systems that have shown this correlation include (1) point mutations in bacteria, (2) point mutations in the X-linked recessive lethal test in Drosophila, and (3) point mutations in mammalian cells in culture. Unscheduled DNA repair synthesis in mammalian cells in culture should also be included in the battery.

There is extensive literature correlating results in bacterial mutagenicity tests and carcinogenicity as determined by chronic toxicity studies (Refs. 17 through 20). This correlation is not perfect, and certain classes of carcinogens cannot be detected in mutagenicity assays.

The published data on mutations and DNA repair in eukaryotic cells are not as extensive as data concerning the Ames bacterial mutagenesis tests. The tests in mammalian cells appear to complement those in bacterial cells for the correlation of mutagenicity and carcinogenicity (Ref. 21). Testing in other systems is particularly important when the chemical is toxic to bacteria, as are many animal drugs, especially antibiotics. This toxicity will often make it impossible to test the chemical at a sufficiently high dose for negative results in bacterial tests to be meaningful.

All short-term tests for carcinogenicity should be performed separately in the presence, and in the absence, of a metabolic activation system, generally derived from rodent liver or the liver, or other relevant tissue, of the target animal. When appropriate, metabolites should be treated with glucuronidase and aryl sulfatase before testing.

Due to the rapid advances being made in the field (Refs. 22 through 34), it would be inappropriate for this proposal to prescribe or recommend detailed protocols for each general type of test. At the present time the most reliable, perhaps the best, results are obtained with the plate incorporation assay described by Ames (Ref. 22).

Application of the screening tests for scoring factor 3 requires some knowledge about the composition of the total residue to determine which residues should be subjected to the complete battery of tests. Although the sponsored compound should always be subjected to the complete battery of tests, for some or all metabolites it may sometimes suffice to perform less extensive testing, e.g., bacterial testing only. The sponsor should explain the reasons for selecting certain metabolites for testing and the reasons for not testing others. Similarly, use of an incomplete battery of tests should be explained. Factors such as structure and residue concentration in tissue should be addressed. In addition, a reduction in testing for any major metabolites should be justified based on factors such as the structural relationship to more exensively tested compounds.

Because of evidence that some structural classes of carcinogens may not yield a positive response in the short-term tests, there will be cases when results from such tests cannot be accepted.

(c) Other biological and pharmacological data: The sponsor should provide the results of a literature search on the sponsored compound and postulated metabolites. This search should also include relevant information on biological activity of structurally related compounds, particularly when very little information is available on the sponsored compound. The sponsor should also include and discuss any relevant information on the pharmacologic and physiologic activity, such as studies that may provide clues regarding the mode of action and expected toxicity. Frequently, in support of the investigational use for the chemical, the sponsor will have gathered some information on pharmacolo-

01183

gic and physiologic activity and will also have developed subchronic test data in experimental animals, e.g., 90-day rodent and nonrodent studies. The data must be submitted for incorporation in the threshold assessment.

The foregoing types of information will be analyzed in the threshold assessment to identify any evidence suggesting that the sponsored compound or its expected metabolites is carcinogenic. This evidence will include findings of hyperplasia or of an abnormal proliferation of any type of cells. These findings lead to a suspicion of carcinogenic potential because such changes have frequently been shown to progress to cancer in studies of longer duration. Also, suspicion is raised by evidence of liver or kidney necrosis and evidence of the formation of regenerative nodules. Certain endometrial changes may also be indicative of possible preneoplastic effects (Ref. 35).

Other examples of biological information raising a suspicion of carcinogenic potential of a compound or its metabolites are binding to cellular nucleophiles, or an indication of the alteration of nucleic acid. Estrogenic compounds will be considered to be suspect carcinogens. Any compound that has the ability to disturb normal hormonal balance, a fact that may be known from pharmacologic studies, or that may be suspected from the organ effects observed in short-term toxicity studies, will be of carcinogenic concern.

4. *Scoring system and the threshold decision.* After the threshold assessment has been completed, each compound is assigned a scoring number that is determined by multiplying score factor 1 (use) times score factor 2 (amount of the residue) times score factor 3 (structure/biological activity). A compound with a score number above 1,000 raises enough concern about the potential contamination of food with carcinogenic residues that is must at least enter the first step of data collection specified by the regulations. The data collection process for a sponsored compound receiving a score equal to or less than 1,000 begins in accordance with the requirements (for risks other than cancer of the general safety provisions of the act. If, at any time after this data collection process begins, the data show that the risk of cancer is greater than that indicated by the threshold assessment score, the sponsored compound will become subject to these regulations.

Table V below shows the maximum concentrations of total residues of toxicological concern that could be found in the most efficient accumulator among the edible tissues and the corresponding scores of factors 1 and 3 that together would permit a sponsored compound to be exempt from the requirements of the regulation.

TABLE V—THRESHOLD ASSESSMENT*

Use (factor 1)	Residue maximum (factor 2) parts per billion	Structure/ biological activity (factor 3)
1	1,000	1
1	100	10
1	10	100
10	100	1
10	10	10
10	1	100
100	10	1
100	1	10
100	0.1	100

*Maximum concentration of total residue of toxicological concern that could be found in the most efficient accumulator among the edible tissues and the corresponding score of factors 1 and 3 that would permit sponsored compounds to be exempted from the regulations.

III. METABOLIC STUDY IN TARGET ANIMALS TO IDENTIFY RESIDUES OF CONCERN

A. NEED TO IDENTIFY RESIDUES IN EDIBLE TISSUES

Before any decision can be made concerning conditions of safe use of a sponsored compound, it is necessary to obtain information on the residues that occur in edible tissues when the compound is administered to the animals for which it is intended (target animals). Without such information, informed decisions about human safety regarding edible tissues derived form treated animals are not possible.

A substance administered to target animals is not necessarily the substance consumed by persons who eat the edible products of target animals. The enzymatic system or physiological fluids of an animal can act upon a compound administered to the animal and produce new compounds in the process (metabolites and degradation products of the sponsored compound). Therefore, the sponsored compound is not the only tissue residue of concern. Sections 512(b)(7) and 512(d)(2) of the act explicitly provide that, before approving its use, the Commissioner must consider the safety of any substance formed in or on food by a sponsored compound. The toxicity of substances derived from a sponsored compound (metabolites and degradation products) is not necessarily of the same magnitude and type as the toxicity of the parent compound, i.e., some metabolites may be considerable more toxic and some considerably less toxic (Refs. 36, 37, 38). Moreover, metabolites of the sponsored compound that were at one time considered "detoxification" products of the target animals (e.g., glutathione conjugates, mercapturic acid conjugates, and sulfates) actually may represent a hazard when consumed by humans (Ref. 38).

Numerous comments were received on the requirements of the 1973 and 1977 notices for metabolic studies. Several comments stated that no attention should be paid to metabolites. Other contended that metabolism studies should not be routinely required, on the ground that the pathway of excretion is of no toxicological importance if all the administered compound has been eliminated from the tissues of the target animal. Most comments recommended that a metabolism study be required only to determine the major metabolites in the edible tissue of target animals; they suggested that the public health would not be served if sponsors were required to pursue endless structural elucidations and quantitations of all metabolites even though some of them might constitute minor fractions of the total residue of the sponsored compound. Comments also contended that it may not be experimentally possible to administer to animals sufficient quantities of a compound to obtain adequate amounts of residues for structural identification. Several comments asserted that studies should be limited to identification of residues in the edible tissues of target animals and that generally it would be unnecessary to have this information on metabolites in inedible tissues. Further, some comments stated that radiotracer studies can be employed to determine the time by which the sponsored compound and its metabolic products are eliminated ("out time"). However, many other comments suggested that all metabolites be identified and tested for toxicity.

The Commission reiterates that metabolic studies are necessary to assure that sufficient information on residues is collected to permit a food safety evaluation, which in turn can be used to establish criteria for regulatory assays. Therefore, the Commissioner has concluded that the metabolic studies discussed below in this preamble are necessary to determine whether the proposed use of a sponsored compound is safe. Also rejected are the arguments that the agency can consider, under the Delaney clause, only the carcinogenic potential of the sponsored (parent) compound. The Commissioner concludes that industry argument that metabolites of the sponsored compound are excluded from regulation under the Delaney clause and covered only by the general safety provisions of the act rests on a strained reading of the act, which ignores the language and purpose of the Delaney clause. A substance may properly be said to induce cancer when it or any substance which it may become through metabolism induces cancer. Consequently, in determining whether a substance induces cancer, it is appro-

01184

priate—and in accordance with the congressional purpose of protecting the human food supply from added carcinogens—to examine metabolites as well as parent compounds.

Further, even if the Delaney clause were inapplicable to metabolites, the general safety standard would still apply, i.e., it imposes the same requirements that the Delaney clause imposes. So even if the industry argument were correct, it would not change the regulatory outcome. Nevertheless, the industry argument also illustrates that the general safety provisions encompass the anticancer clauses of the act. Assessment of a compound's safety requires a comprehensive examination of the sponsored compound and all of its metabolites and breakdown products. To the extent that the language in § 514.1 (21 CFR 514.1) implies a different view, the Commissioner is proposing to reword that regulation to correct any possible misunderstanding.

B. CONDUCT OF METABOLIC STUDY

1. *Test animals.* The metabolic fate of an administered compound in an animal may be unique for each livestock production class. Therefore, the Commissioner concludes that a metabolic study in the animals for which a sponsored compound is intended (target animals) is necessary. If the petitioner can demonstrate that the data from the metabolic study obtained for one production class are applicable to a second, the Commissioner may modify the extent of the investigation required for the latter.

2. *Required technology.* The metabolic fate of a compound administered to food-producing animals is pivotal in determining the need for and extent of carcinogenesis testing. It is mandatory that the metabolic fate be adequately determined. It is necessary that residues of potential carcinogenic significance have been detected at levels obtainable by the best analytical technology available. Therefore, the Commissioner concludes that the required metabolic studies must be conducted with the best analytical methods that technology provides.

As set forth in part VI of this preamble, one residue must be selected to serve as a practical indicator to assure that the "no-residue" standard of the act is met. This residue can be selected only by reference to a metabolic study in which residues are detected and measured at levels dictated by the outcome of actual carcinogenicity testing. Because these levels cannot be known at the outset of this phase of the metabolic study in target animals and because the "best available technology" may not be adequate to measure the levels dictated by the outcome of carcinogenicity testing, it may be necessary to develop improved technology and to repeat the metabolic study in target animals after carcinogenicity testing has been completed. Another requirement of the second metabolic study will be the collection of enough data to construct tissue concentration-time profiles for some residues.

3. *Analytical techniques.* For the foreseeable future, the general technique of choice for metabolic studies will be the use of radiotracers. The proposed regulations, therefore, consistent with principles that assure scientific quality, recommend that the required metabolic studies be conducted with radiolabeled compounds of the highest specific activity available. These principles concern the types, the chemical nature, the chemical and metabolic stability, and the suitability of radiolabels for metabolic studies having specific objectives. The principles have been developed from past metabolic studies with radiotracers, and adherence to them ensures the scientific quality of the required metabolic studies (Refs. 39 and 40).

The task of residue detection can often be made easier by available information on the metabolism of related compounds. It is recommended that proposed metabolic pathways which appear applicable to the sponsored compound be based on relevant literature references about compounds of similar structure. This information can usually simplify the choice of radiolabel positions, which will ensure that all residues containing structural moieties of potential toxicological concern can be detected. However, these projections of likely metabolism can never be a substitute for experimental observation of the metabolic fate of the sponsored compound.

Although use of radiotracers is the preferred experimental procedure, some compounds possess inherent physicochemical characteristics (e.g., strong fluorescence associated with the structural moiety of potential toxicological significance) that will allow the necessary detection of residues. In such cases, the use of radiolabels may not be required.

4. *Dose regimen.* The dosing regimen for the metabolic study in the target animals must be consistent with the maximum proposed use level and duration of exposure to the sponsored compound. For compounds administered continuously over long periods of time, administration for the metabolic study need continue only until equilibration or saturation of edible tissues has been demonstrated. If tissue equilibration cannot be shown, the sponsor must show that the pattern of residues has stabilized.

The metabolic fate of a compound administered to target animals is likely to depend on the conditions (level, method, and duration) of use (Refs. 41 and 42). Because the purpose of the required metabolic studies is to characterize and quantitate residues under conditions of proposed use, these conditions must be followed in the metabolic studies. However, it is possible that under these conditions certain residues are produced in amounts that do not allow extensive chemical characterization. If the structure of any such residues must be determined, and if sufficient amounts of residues can be produced by administering larger doses of the sponsored compound to target animals, the petitioner would be allowed to follow this procedure. In some instances, chemical synthesis of residues may be easier.

5. *Required data.* Because the relative persistence of residues in edible tissues (i.e., the likelihood that residues will be found in edible tissue) is one consideration in selecting specific residues for toxicity testing, the proposed regulations require that the total number and the relative quantities of residues be determined immediately following cessation of treatment, as well as at a sufficient number of intervals after the initial measurement to determine the depletion trend of individual residues. The number of these measurements needed to identify depletion trends depends upon the kinetics of depletion of the sponsored compound, and for this reason the complete extent of data collection cannot be specified in advance.

The need for, and extent of, chemical characterization of residues depends on a number of factors. Ordinarily, compounds constituting a significant fraction of the total residue require sufficient physical and chemical characterization to permit a determination of whether or not a structural change has taken place that could increase the carcinogenic potency of the residue over that expected of the sponsored compound, e.g., formation of epoxides from olefins, N-hydroxylation of aromatic amines, cyclization of hydroxyacids to suspect lactones (Refs. 14 and 15). In some instances, it may be impossible to judge whether the residue has carcinogenic potential, but sufficient structural alteration alone may be enough to establish the need for further characterization. Because these structural changes are common during metabolism and because it is the tissue residues to which human beings potentially will be exposed, this characterization will normally be required. When the agency determines that a component of the residue requires chronic toxicity testing (because of tissue concentration and persistence and/or expectation of increased carcinogenic potential), chemical characterization and an effort to obtain sufficient quantities of

01185

the residue(s) for toxicity testing will be necessary. (See, however, section III.C., below.)

Residues that appear to become "bound" to tissue components (i.e., those whose rate of depletion appears to be no greater than the turnover rates of tissue components) cannot be automatically exempted from the requirements of the regulation. These residues may be hazardous to humans ingesting edible tissues. The residues can be identified by a variety of standard techniques (Refs. 44, 45, and 46). Of course, any such residue will be exempt from the regulation's requirements if it can be shown that it is a normal tissue constituent deriving from a metabolite of the sponsored compound that has entered normal pathways of intermediary metabolism of target animals (Ref. 43).

In some instances, a sponsor may be required to pursue the complete characterization of certain relatively minor metabolites if partial physiochemical characterization indicates that a structural change during metabolism in the target animal has introduced molecular moieties of carcinogenic potential greater than that expected of the sponsored compound, e.g., nitrosation of an amine of unknown carcinogenic potential to produce nitrosamines of known carcingenic potential (Refs. 14 and 47).

Because uncharacterized tissue residues may pose a risk to public health, the proposed regulation would require that the procedures for separation, purification, characterization, and identification be consistent with the best available scientific and technological capabilities. Ordinarily, the agency will require attempts at characterization to include use of a variety of procedures based on the various forms of chromatography, spectroscopy, and spectrometry.

Allegations have been made that the regulations impose unreasonable requirements (i.e., that the regulations require inordinately complex, and therefore costly, experimental procedures) and that the information to be gained from these tests is not worth the costs of gathering it. Both allegations either ignore the current state of these sciences or misunderstand the requirements of the proposed regulations. All the procedures described in the proposal are standard techniques that are widely used in basic biochemistry and pharmacology investigations. A few comments showed confusion about the requirements associated with the metabolite identification study. To correct any potential misunderstanding, the Commissioner has eliminated the earlier requirement that all residues of the sponsored compound be identified until the sponsored compound has been depleted for three half-lives in the target animals. A safety assessment requires information on the trends of residue depletion in the target animal's tissues. Therefore, the Commissioner proposes to substitute the requirement that residues be identified at sufficient intervals to permit determination of the trends of depletion of individual tissue residues.

6. *Format for data submission.* The Commissioner has concluded that the format for presenting results of metabolic studies should be standardized to minimize the possibility of misinterpreting the data. Because these studies will be the basis for major public health decisions, the Commissioner considers it essential that they be carried out and reported in keeping with the best available criteria. The two professional societies listed in the proposed regulations (American Chemical Society and American Society of Biological Chemists) follow policies for accepting manuscripts that embody the best available criteria for collecting, interpreting, and reporting scientific data of the type required by this regulation.

C. COMPARATIVE METABOLISM STUDY TO AID IN ASSESSING CARCINOGENICITY OF INTRACTABLE RESIDUES

1. *Sponsored compound always tested: rationale and procedure.* The sponsored compound itself must always be tested for carcinogenesis when it is determined on the basis of the threshold assessment and the initial metabolism study required by the regulation that a sponsored compound has the potential to contaminate edible tissues with residues whose consumption may pose a human risk of carcinogenesis. Even if the sponsored compound is not detected among the residues, there are compelling reasons for testing the sponsored compound in addition to testing any residues identified according to the criteria already discussed in section III.B above. Metabolic transformation or nonenzymatic degradation of a sponsored compound can lead to a number of tissue residues that cannot be obtained (either by isolation or synthesis) in sufficient amounts for carcinogenicity testing. (These residues are referred to in this document as "intractable residues".) Testing the sponsored compound itself, therefore, provides an experimental means for acquiring data bearing on the carcinogenic potential of such residues.

Although the dominant criterion for selecting test animal species or strains for chronic toxicity testing will be the degree to which a species or strain models man, applying a secondary criterion for selection can help to address the problem of intractable residues. Specifically selection of test animals can also be based on comparative metabolism data (target animal versus test animal). These data can be used to determine the extent to which particular species or strains, due to the way they metabolically convert the sponsored compound, will be exposed during testing to the same complement of residues to which man may be exposed in tissues derived from target animals.

For example, if a metabolite detected as a residue in edible tissues of the target animal is determined to be toxicologically important, the sponsor will be asked to isolate or synthesize the compound for purposes of toxicity testing. If all such attempts fail, then the comparative metabolism approach is available if a potential test animal species, when adminstered the sponsored compound, is shown to produce the same metabolite. There is thus some assurance that the toxicity test of the sponsored compound also provides an estimate of the toxicity of the intractable metabolite. Because human food could be contaminated with the intractable metabolite, this test is a practical approach to a complex and important issue.

This construct was included in the February 1977 notice in response to comments that either suggested that all metabolites ought to be ignored (which the Commissioner concludes is neither legally nor scientifically acceptable) or that all metabolites must be isolated and independently tested (which is not always possible, for technical reasons). Further, the Commissioner invited additional comment on this construct.

Comments on the use of comparative metabolism to deal with intractable residues addressed several points: the definition of "intractable residues," the criteria for determining whether a test species will produce the same complement of intractable residues as the target animals, the basis for treating tractable and intractable residues differently for chronic testing, and the potential use of "relay" toxicity testing.

One comment misinterpreted the definition of "intractable residues." It suggested that they are substances about which nothing is known. The regulation, however, proposes to define the term "intractable residues" as those that either cannot be isolated from biological material or cannot be synthesized for purposes of further testing. The experiments that will already have been conducted for determining the presence of intractable residues (e.g., chromatographic and spectroscopic experiments) will furnish considerable information about the physical and chemical characteristics of the residues. Accordingly, basic techniques of biochemistry and phar-

01186

macology can determine whether the test animal species will be exposed to the same complement of residues that appear in the target animals' tissues. These techniques will ordinarily supply enough information to make such an evaluation. Therefore, the Commissioner concludes that the comparative metabolism studies have merit for the purpose of dealing with intractable residues.

The Commissioner established a series of requirements that can be satisfied by different experimental techniques having varying degrees of rigor. To avoid multiple interpretations of the same set of experimental observations, the Commissioner concluded that there must be established an additional general requirement that the experimental technique with the greatest degree of rigor be the one used for metabolic studies, and the agency adopted the term "best available technology" to describe this requirement. Thus, if the nature of residues can be determined by ultraviolet spectroscopy (a method of very low specificity) or by mass spectrometry (a method of high specificity) the Commissioner will require the use of the mass spectrometric method.

The Commissioner rejects the suggestion that all compounds be treated as the intractable residues are. Animal bioassay of specific metabolites is the best method of determining potential for chronic toxicity, and the Commissioner would prefer to have all metabolites chronically tested. However, recognizing the limitations of organic synthesis, separation sciences, and facilities available to conduct long-term bioassays in animals, the Commissioner has settled for using comparative metabolism for safety assessment of those residues requiring the application of techniques beyond the bounds of the best available technology. Nevertheless, sponsors will be held to the task of conducting the best type of toxicity study for selected residues that are susceptible to identification and isolation, or synthesis, by the best available technology. Although deeming it essential that sponsors pursue those goals with the best science and technology available, the Commissioner recognizes that the somewhat less than ideal toxicity assessment rendered by the comparative metabolism approach is useful for intractable residues. This position is a reasonable balance between completely ignoring all intractable residues and requiring their pursuit in the absence of the necessary technology.

One comment suggested feeding to test animals the contaminated tissues from treated target animals to assess the safety of residues to which humans will be exposed ("relay" toxicity testing). The Commissioner rejects using relay testing because it has two important limitations. Practical animal testing is limited to a relatively small number of animals as surrogates for the entire human population, and the only way to overcome the known limitations of such bioassays is to feed the small number of animals levels of the test compounds that are far in excess of the levels of animal drug residues to which humans are expected to be exposed. Because tissues of animals do not contain residue levels sufficiently high to compensate for the known limitations of standard bioassays and because they therefore are not a suitable basis for evaluating the residue's carcinogenic potency, as that term is used in this notice, the Commissioner must reject the use of relay toxicity testing. Further, the direct use of tissues from treated animals as test material does not permit determining which, if any, specific residues are responsible for the observed effects and the contribution of the residues to the effects.

Data collected according to the procedures and criteria above will: (i) Establish the number of metabolities in target animals and in a number of species/strains of test animals; (ii) provide information about the chemical structure of these metabolities (the structure of some metabolities will be known completely although for others only partial information will be available); (iii) provide information about the persistence of these metabolities in tissues; and (iv) provide information about their mutagenic, cell transformation, or their DNA damage potentialities. This information will permit FDA to classify the residues into the tractable and intractable categories, to select from the category of tractable residues those that must be subjected to chronic toxicity testing, and to document this selction. Criteria for classifying residues into the tractable and intractable categories were discussed earlier. Criteria for selceting tractable residues for chronic toxicity testing will be discussed in turn below.

First, it is unnecessary to require that all tractable residues be subjected to chonic toxicity testing. Most often, judicious use of well-established biochemical knowledge will eliminate the need for such extensive testing. A good estimate of the carcinogenic potential of the sponsored compound and its metabolities can be obtained without testing each of the tractable metabolities.

Ordinarily, xenobiotics are metabolicly transformed by target animals, test animals, and man in sequences of enzyme-catalyzed reactions, with considerable interspecies similarities (Ref. 48). The described metabolic studies, especially the studies in comparative metabolism, will provide significant information about these reaction sequences and there interspecies similarities.

It is obviously unnecessary to subject to independent chronic toxicity testing intermediates in sequences that are reasonable expected to be similar in man and the selected species of test animals, and which also are residues in target animal tissues. Testing the leading substrate of each sequence will be sufficient. Tractable residues in target animals that are not produced by the selected test animal species must be tested independently in the absence of information that they are not carcinogenic.

Finally, to estimate reasonably the carcinogenic poetential of the sponsored compound and its metabolites in target animal tissues, one must eliminate the confounding effects of metabolites or sequences of biotransformation reactions unique to the chosen test animal species. These metabolities, if present, could be subjected to short-term tests (mutagenicity, cell transformation, or DNA repair) to assess their inherent potential to produce irreversible effects when in intimate contact with tissues and tissue components. Negative findings would eliminate these residues from further consideration as factors likely to confound the results of bioassays. Further, if these residues are known or expected to be common to the chosen test animals and man, negative findings would eliminate them from the residues of toxicological (in this instance carcinogenic) concern. On the other hand, a positive finding would be a clear indication that they are prime candidates as the causative agents of adverse findings in test animals.

2. *Selection of residues for chronic toxicity testing.* Based on all the studies described above, the Commissioner will select those residues, in addition to the sponsored compound, that require chronic toxicity testing.

IV. Chronic Toxicity Testing

The sponsored compound and any residues selected for testing must be subjected to oral, lifetime, dose-response studies in two of the test animal species strains selected under the criteria described in the foregoing paragraphs. The purpose of these studies is to determine whether the compounds under test are carcinogenic and, if so, to establish the lowest limit of reliable measurement that must be achieved by any regulatory assay for monitoring residues resulting from use of the sponsored compound.

Several comments on this feature dealt with testing chemical compounds for carcinogenic potential, and addressed two major issues: (i) The design of chronic studies, and (ii) the

01187

relevance of animal testing in evaluating human safety.

A. DESIGN OF CARCINOGENICITY STUDIES

Comments on the proposal and the notice expressed contrasting opinions on the design features of carcinogenicity studies with experimental animals. The comments specifically addressed: (i) Selection of appropriate test animals; (ii) conditions, levels, and duration of exposure; (iii) statistical design as it relates to number of animals assigned to the various levels of exposure; and (iv) the adequacy of controls.

The impact of these design features on interpreting animal carcinogenesis data is an important and controversial matter currently under intense scientific investigation. The major effort at FDA's National Center for Toxicological Research (NCTR) is specifically aimed at developing relevant protocols and experimental designs for carcinogenicity testing. The agency has also begun to work on supplementing the NCTR effort within the Interagency Regulatory Liaison Group (IRLG). Until these efforts are concluded and the results incorporated into regulations or into official publications, the Commissioner recommends as guidance the report of the Food and Drug Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis, Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides ("Toxicology and Applied Pharmacology," 20:419-438, 1971). This report reviews and analyzes all facets of experimental design that have been developed and scrutinized by competent scientists before 1971. To facilitate incorporating later developments in testing standards as they evolve, the proposed regulations suggest that petitioners submit developed protocols to the Commissioner for review and updating before initiating studies.

B. RELEVANCE OF ANIMAL TESTING IN EVALUATING POTENTIAL FOR HUMAN CARCINOGENESIS

Several comments on this aspect of the regulation dealt with the merits and shortcomings of animal testing as an experimental tool. Some comments pointed out that even animal testing using the best experimental protocols can never prove conclusively that a compound is not carcinogenic, and that under these circumstances some weak carcinogens may escape identification. Other comments expressed the contrasting view that adequate protocols can be devised. Still others questioned the propriety of drawing conclusions about human carcinogenesis from data collected with experimental animals. Additional comments of the same type were received on these issues after the February 1977 notice. None of these comments provided any evidence or argument that persuades the Commissioner to revise any provision of this part of the regulations. Several comments sugested using short-term in vitro tests, singly or as part of a tiered testing system, as a substitute for long-term toxicity testing. One comment stated that the regulation should apply only to directly acting carcinogens and that indirectly acting carcinogens should be treated differently.

The act requires that in assessing the safety of animal drugs the carcinogenic potential of residues be evaluated. Ordinarily, the evaluation must be based on appropriate testing. Given the gravity of the decisions that depend on the results of these evaluations, the most relevant scientific information must be collected. As a source of information, direct carcinogenesis testing of chemical compounds in man is and must remain beyond the ethical bounds placed by society on human experimentation. Without this information source, which would be the most relevant, alternative sources are human epidemiology studies and animal experimentation. Human epidemiology may provide post facto information about the carcinogenic effects of chemical compounds on man. However, this experience cannot be the central basis for food safety valuations for several reasons, including the inherent imprecision of human epidemiology and the same ethical objections that make direct experimentation in man unacceptable.

There may be a high degree of confidence that a compound found to be a carcinogen in an epidemiology study is a human carcinogen because no interspecies extrapolation is required. However, so-called "negative" epidemiology data (data not showing carcinogenesis associated with a substance) are generally inadequate to overcome positive evidence of carcinogenesis from an animal study. Sources of data are often inadequate for identifying a specific exposed human population. Human beings are exposed to multiple potential carcinogens, and it is difficult or impossible to distinguish their several effects. Moreover, the precise amount of human exposure to particular substances is rarely known. Thus, limitations on the use of epidemiology data include (1) the degree to which the study population can be defined in terms of potential exposure, number exposed to the suspected risk, and the length of the observation intervals, (2) the degree to which the "standard" population used as the control is comparable to the study population, and (3) the role of other factors that might be related to different carcinogenic responses. Further, seldom are there sufficient numbers of subjects available to permit broad-scale conclusions.

The degree to which study populations can be characterized by the level of exposure to specific carcinogens will ordinarily vary considerably because of the lack of measurement in the early years of exposure. Comparison of exposed populations requires contrasting morbidity and mortality statistics of a target population with those of a "standard" population. However, the validity of any conclusion reached from these comparisons depends upon the extent to which other variables related to cancer incidence can be matched, adjusted, or accounted for in the analysis. These controls on data are costly, time consuming, and fraught with imprecision. Finally, detailed human pathology, which is important in demonstrating the role of specific carcinogens in the induction of rare tumors, is seldom available.

The Commissioner therefore concludes that the agency must continue to rely on animal testing for evaluating the safety for humans of chemical compounds proposed for use in food-producing animals. Extensive evidence substantiates this view (Refs. 13, 49, and 50). Consequently, the use of animal tests is generally recognized and accepted by regulatory agencies as the principal basis for assessing potential risks from exposure to chemicals (Refs. 51, 52, and 53). This basis has been universally recognized and accepted by the courts (see e.g. *EDF* v. *EPA*, 510 F. 2d 1292 (D.C. Cir. 1975)). Moreover, the act does not distinguish beteen human carcinogens and compounds demonstrated to be carcinogenic in test animals. Instead, it assumes that an animal carcinogen presents an unacceptable risk of cancer in human beings. In this context, the issue of relevance to man of data from tests in animals must be refocused. In view of the strong policy in the general safety provisions of the act, which includes the Delaney clause, the primary regulatory objective must be to avoid falsely negative determinations of the carcinogenic potential of compounds under test in experimental animals. In this setting, the agency's only tenable regulatory posture is to select bioassay protocols that utilize test animal species/strains that are considered the best surrogates for man. The selection is based on available toxicologic and metabolic information.

Numerous terms are used to describe various proposed mechanisms of induction of chemical carcinogenesis, e.g., direct carcinogens, indirect carcinogens, promoter, initiators, cocarcinogens. The current knowledge of the mechanism of chemical induction of cance is generally not adequate to

01188

permit these subtle distinctions. Further, the types of scientific studies necessary to identify precise modes of action for specific carcinogens are not yet refined to the point that they can be commonly applied (Ref. 54).

Moreover, the act does not distinguish between so-called "direct" and "indirect" carcinogens, and all types (assuming they are experimentally distinguishable) pose the same kinds of health risk to the public—namely, the risk of human cancer—that the act seeks to prevent. Therefore, the Commissioner concludes that there is generally no scientific basis for making regulatory distinctions among carcinogens.

The Commissioner agrees that short-term in vitro tests have a place in assessing the carcinogenicity of chemicals, as described in the preceding sections of this preamble, when they are intelligently applied and interpreted. However, the Commissioner does not agree that these tests can now substitute for long—term bioassays. The reasons for this conclusion were articulated by the expert committee on the National Cancer Institute on the use of these tests (Ref. 13).

At present, none of the short-term tests can be used to establish whether a compound will or will not be carcinogenic in humans or experimental animals. Positive results obtained in these systems suggest extensive testing of the agent in long-term animal bioassays, particularly if there are other reasons for testing. Negative results in a short-term test, however, do not establish the safety of the agent.

C. INTERPRETATION OF TEST DATA—IS THE COMPOUND A CARCINOGEN?

The majority of comments on the February 1977 notice requested greater specificity concerning classification of sponsored compounds as carcinogens, potential or suspect carcinogens, and noncarcinogens.

The objective of collecting and interpreting test data is to decide whether or not the compounds under test (the sponsored compound and any selected metabolites) are carcinogens. Within certain limits of confidence, statistical treatment of chemical carcinogenesis data can provide objective criteria for such determinations. To the question "Is the tested compound a test-animal carcinogen?" statistics can supply one of two types of answer:

(i) With "x" percent confidence (i.e., in "x" cases out of 100), "y" dose of the test compound will increase the carcinogenesis risk of test-animals over controls by no more than "s" and no less that "t"; or

(ii) With "x" percent confidence, "y" dose of the test compound will increase the carcinogenesis risk of test animals over controls by not more than "s."

An answer of the first type is possible only when the observed incidence of carcinogenesis in the test animals is significantly greater than that in the controls. When the observed incidence is the same for test and control animals, only an answer of the second type is possible.

A statistically significant increase in the incidence of carcinogenesis in one species or strain of test animals (i.e., an answer of the first type) is sufficient evidence to classify the test compound as a test-animal carcinogen. Because, for the purpose of these regulations, the act does not distinguish between human and animal carcinogens, a test compound as a test-animal carcinogen brings into play the requirements of the anticancer clause.

If the animal test data will permit only an answer of the type, the decision whether to classify the test compound as a test-animal carcinogen is more difficult. A negative test finding, as pointed out in some comments, can mean either that the test compound is not a test-animal carcinogen of that the bioassay protocol lacks a sufficient number of animals to discern an increase in the risk of carcinogenesis in the test animals. In those cases, a decision must be made whether to classify a tested compound as a noncarcinogen or to require further experimentation appropriate for resolving questions of safety. The Commissioner will conclude that a sponsored compound is not a carcinogen if the sponsored compound and each of the tested metabolites yields negative results. For purposes of these regulations, the Commissioner is proposing that the absence of a significant increase in tumor incidence in each of two different animal bioassays, conducted in accordance with good laboratory practices and designed according to principles referenced above, is (in the absence of other, positive data) sufficient evidence of noncarcinogenicity.

V. OPERATIONAL DEFINITION OF THE NO-RESIDUE REQUIREMENT

A. ALTERNATE OPERATIONAL DEFINITIONS

If it has been determined that a sponsored compound when admnistered to food-producing animals has the potential to contaminate edible tissue with residues whose consumption may pose a risk to human carcinogenesis, the agency cannot approve the sponsored compound unless it can be demonstrated that conditions of use can be established that ensure that the no-residue requirement of the act will be met. To establish those conditions of use and to provide a means for ascertaining whether these conditions are met in actual practice, some operational definition of "no residue" is necessary. Indeed, the act contemplates that the Commissioner will provide such operational definition, for there must be some criteria for prescribing or approving methods of examination for measuring residues.

The Commissioner has considered three basic alternative approaches to an operational definition of the phrase. Under one approach, the term "no residue" might be operationally defined as satisfied when the levels of residues fall below those that can be measured by available analytical methodology (alternative 1). A second approach would be to establish some low finite level (e.g., 1 part per billion) as a "practical zero" and to require assays that can reliably measure this zero, and to insist on the development of new assays if available assays are not adequate (alternative 2). Finally, "no residue" might be operationally defined on the basis of quantitative carcinogenicity testing of residues and the extrapolation of test data using one of a number of available procedures to arrive at levels that are safe in the total diet of test animals and that would, if they occurred, be considered safe in the total of man. Under this approach, the Commissioner would require assays that can reliably measure that safe level in edible tissues (alternative 3). For the reasons discussed in section V.B. below in this preamble, the Commissioner has concluded that alternative 3 should be adopted. The results of the carcinogenicity testing of the sponsord compound and any selected residues will be treated by the statistical procedures described in section V.

B. CHOICE OF AN OPERATIONAL DEFINITION

1. *Alternative one.* A number of assays might be development to measure the concentration of a chemical compound (i.e., residue) in an edible tissue, but for each there would be some level below which the compound under analysis could not be measured. (See section I.B. of this preamble.) Generally, different assays for the same chemical compound will have different, and sometimes vastly different, lowest limits of measurement. The no-residue requirement of the act could be translated an operational definition that is based solely on available analytical methodology and specifically on the lowest limit of measurement of an available assay. Thus, the degree of public risk associated with the use of a sponsored compound would become a function solely of the capability of available analytical technology.

The Commissioner concludes that this approach is unsound because it ignores all quantitative aspects of carcinogenicity testing. The carcinogenic potency of different chemicals varies widely. As used in this document, the

01189

term "potency" refers to the dose required to produce a given rate of cancer. Disregard of "potency" in developing criteria for evaluating spnsored compounds would scientifically unsound, and would make no sense from the perspective of public health protection in accordance with the Delaney clause and the general safety provisions. Such disregard would produce situations in which residues of different compounds could present widely varying risks. The regulatory assays selected that way would not represent a consistent policy of protecting the human food supply from cancer risks. Indeed, the pattern of protection from one compound to another would be haphazard.

2. *Alternative two.* A second approach that the Commissioner considered was to establish a "practical zero" for the residues of all carcinogens. This approach would have one advantage over alternative one: it would provide a well-defined criterion for the lowest limit of measurement that any sponsor's assay would have to satisfy. This approach also would not, however, take into account differences in carcinogenic "potency" among various carcinogens. (See Table III.) Therefore, it is unacceptable for the same as alternative one. Unless the "practical zero" were set at the level appropriate for the most "potent" carcinogen, it would provide insufficient protection; but if it were set at that level, it might be unnecessarily stringent for carcinogens that produce a response that is of a lower magnitude. In sum, no one "practical zero" is appropriate for all carcinogens.

Moreover, under alternative two, the criterion for lowest limit of measurement probably would reflect consideration of what lowest level of measurement is "practical," given the state of the art analytical chemistry or biochemistry. In addition to failing to link the no-residue standard to any consideration of carcinogenic potency, this approach fails on the ground of practicality. The science and technology of analytical chemistry and biochemistry are continuously changing, and a lowest limit of measurement considered reasonable at one time would have to be discarded as unreasonable at a later time. Whenever a new and lower criterion for the limit of measurement would be established, the Commissioner would then presumably require that use of all compounds approved under the prior criterion be suspended until methods were developed to measure the residues at this lower level. Such a situation, in the Commissioner's judgment, would be both unreasonable and unmanageable.

On the other hand, to disregard advances in analytical chemistry and adhere to a previously established practical lowest level of reliable measurement with no public health rationale for doing so would be contrary to the statutory purpose and, ultimately, arbitrary and capricious.

A modification of the basic "practical zero" also has been suggested, i.e., that Congress intended FDA to adopt a practical zero set at the level of analytical technology at the time the various Delaney clauses were adopted. Under this theory for food additives, the practical zero would be set at the level of technology in 1958; the DES proviso would be governed by the level of technology in 1962; and new animal drugs, by the level in 1968. This uneven floor of technology is inappropriate not only for the reasons that make any "practical zero" level inappropriate, but also because it would be impossible for the agency to administer and has no basis in the policy or legislative history of the various amendments to the act.

3. *Alternative three.* A third approach to defining operationally the no-residue requirement is to establish a required lowest limit of measurement for each sponsored compound on the basis of data derived from measurements of the carcinogenic response resulting from various amounts of the compound itself or selected metabolites (Dose-response studies). A result of the increasing understanding of chemical carcinogenesis is that the question asked is no longer merely whether a substance is a carcinogen, but what is the amount required to produce a given incidence of cancer (Ref. 55). This concept of a dose-response relationship has long been used in medicine to determine safe and effective does of therapeutic agents. It is customarily used to describe the commonplace observation that in the majority of cases, different quantities of two different pharmacological agents are needed to elicit the same pharmacological effect (relative potency) (Ref. 56).

Both pharmacological effects and carcinogenic effects are biological effects, and there is no a priori reasons why the concept of relative potency should apply to the former but not to the latter. Carcinogenesis bioassays of increasing refinement conducted over the last 20 or so years have borne out this notion of relative potency for carcinogens. Thus, scientists ever more frequently speak of weak and strong carcinogens. In doing so, they express what is implied by the observation, for example, that dietary exposure to comparatively small amounts of 2-acetylamino fluorine causes bladder cancer in rodents at the same rate as does exposure to comparatively large dietary amounts of saccharin. Under this approach, relative carcinogenic potency is given specific consideration because actual chronic toxicity test data are used to determine the level of residues in edible tissue that an assay must be capable of measuring reliably. Thus, it permits a rational, uniform procedure for establishing the required lowest limit of measurement for assays and avoids the major deficiencies inherent in alternatives one and two. This approach directly carries out the statutory purpose of protecting the human food supply from residues that pose a carcinogenic risk to man.

Should new information develop on the dose-response relationship between the level of residues of a sponsored compound and the incidence of cancer, this approach would provide a practical basis for determining whether a new assay is required to establish compliance with the no-residue standard. Thus, this approach contributes to regulatory stability and predictability. Likewise, the Commissioner can provide the maximum public-health protection based on quantitative carcinogenesis data. For these reasons, the Commissioner concludes that alternative three is the most appropriate means for implementing the statute and the most rational approach to developing an operational definition of "no residue."

By adopting this approach to implementing the no-residue standard, the Commissioner has assumed that: (i) The dose-response relationship between chemical compounds and carcinogenesis can be quantified, and (ii) a dietary level of a carcinogen can be identified at which no significant human risk of carcinogenesis would derive from consuming food containing residues below this level.

The dose-response relationships between compounds and carcinogenesis can be determined by testing in experimental animals, although the determinations are subject to known limitations inherent in every measuring device or system (Ref. 11). The second assumption, that residue levels representing no significant human risk of carcinogenesis can be assigned, protects the public from the potential and real dangers inherent in the interpretations of the "no-residue" standard of the act discussed as alternatives one and two. This second assumption and related issues are fully discussed in the next section of this preamble.

C. ANALYSIS OF ANIMAL CARCINOGENESIS DATA TO DEFINE OPERATIONALLY THE "NO RESIDUE" STANDARD OF THE ACT.

1. *Introduction.* The 1973 proposal included a modified version of the extrapolation procedure of Mantel and Bryan 1961 for use in defining the "no residue" standard for a sponsored compound (Refs. 57 and 58). The 1977 notice adopted a modified version of

01190

the Mantel et al. 1975 procedure, which updated the 1961 procedure. The basic Mantel-Bryan procedure is one of several statistical techniques that allow estimation of the level, or dose, of a carcinogen that would lead to cancer rates in test animals well below detectable rates in practical experimentation. In normal experiments in which test animals are administered various levels (doses) of a suspected carcinogen, the observed responses (i.e., the percentage of test animals developing cancer if the compound is a carcinogen) usually range from about 5 percent to 95 percent. To observe responses at rates less than about 5 percent would require many test animals. Experiments designed to observe responses in the range of interest in establishing the "no residue" standard would require impossibly large populations of test animals. Therefore, the procedures of Mantel and Bryan and Mantel et al., as modified, were proposed respectively to be used in the statistical treatment of the dose-response data from actual experimentation to estimate the dose of the compound under test that would result in lifetime test-animal cancer rates no higher than a preselected rate.

Some operational zero must be defined in order for the "no residue" requirement of the act to be implemented. Regardless of the arguments for or against any particular procedure, the Commissioner maintains that the use of some procedure that quantitatively takes into account the carcinogenic potency of substances in test animals is far superior to any approach that fails to take that fact into account.

The modified Mantel-Bryan procedure described in the 1973 proposal was labeled excessively conservative (i.e., too protective of the public health) by some comments and recklessly liberal (i.e., insufficiently protective of the public health) by others. Those who considered the procedure too conservative objected to the proposed use of a series of conservative assumptions (shallow-slope dose-response relations, low acceptable level of risk, use of upper 99 percent confidence limits, etc.) and contended that any one of these assumptions alone could provide adequate public health protection. Further, these comments argued that the practical application of the procedyre had not been demonstrated, and suggested that it would prohibit the use of many valuable compounds.

Persons who considered the procedure too liberal objected to the proposed use of a lower confidence limit on the observed slope of the dose-response curve. They protested that the proposed statistical technique for extrapolating dose-response data obtained from animal tests seriously underestimated public risk. The technique provides a basis for establishing a dose level where there is no significant human risk of cancer, thereby establishing a criterion for a residue detection method. Specifically, the comments contended that if the true dose-response follows a logistic or linear distribution, extrapolation with the slope from a probit transformation would seriously underestimate public risk. Further, these comments argued that the probit transformation leads to a paradox because strong carcinogens are treated less conservatively than weak ones.

2. *Choice of the statistical procedure.* Most of the comments concerning the statistical procedure proposed in 1973 favored adoption of the Mantel-Bryan procedure without the modifications suggested in the proposal. A smaller number of comments contended that a linear extrapolation would be better than the Mantel-Bryan procedure and even fewer suggested the logistic or the angle distributions. Still other comments suggested that FDA require a comparative analysis of animal carcinogenesis data employing all alternative distributions, and that the smallest estimate of the "safe" level be used to define the "no-residue" standard for a compound. Finally, some comments stated that, although the logistic and angle distributions have been used in biological sciences, there is no indication that either one provides advantages over the probit (Mantel-Bryan) or the linear distribution, and that, therefore, neither is appropriate for regulatory purposes.

Some comments favoring the Mantel-Bryan procedure argued that it has a theoretical rationale that probably is relevant to the carcinogenic action of chemical agents. A similar argument was made by some of the comments favoring linear extrapolation. These comments also contended that linear extrapolation has the public health advantage of being the most conservative of all procedures.

In the period 1973 through 1977, the Commissioner extensively reviewed the known procedures that may be used to derive an operational definition of the no-residue standards of the act from animal carcinogenesis data. This review persuaded the Commissioner that the same scientific and technical limitations are common to all. Specifically, because the mechanism of chemical carcinogenesis is not sufficiently understood, none of the procedures has a fully adequate biological rationale. All require extrapolation of risk-dose relations from responses in the observable range to that segment of the dose-response curve where the responses are not observable. Matters are further complicated by the fact that the risk-dose relations assumed by the various procedures are practically indistinguishable in the observable range of risk (5 percent to 95 percent incidence) but diverge substantially in their projections of risks in the unobservable range.

In the 1977 notice, the Commissioner concluded that the comments failed to demonstrate that another procedure was superior to that of Mantel and Bryan and Mantel et al., and the Commissioner therefore adopted it with some modifications. Moreover, the Commissioner concluded that some aspects of the Mantel-Bryan procedure offered advantages over the other statistical procedures. It provided a means for pooling data from multiple experiments and from multiple dose levels within a single experiment, and thus permitted decisions based on the fullest use of available data. Further, the Mantel-Bryan procedure had a defined mechanism for handling the spontaneous tumor rate. To overcome certain limitations of the Mantel-Bryan procedure, the Commissioner adopted a number of modifications, which were discribed and discussed in the 1977 notice. The Commissioner also concluded that a review of the decision should be undertaken in 2 years and any appropriate modifications in the regulation initiated.

Since publication of the February 1977 notice, the Commissioner has received many additional comments on the statistical procedure chosen. Several suggested that the adopted Mantel-Bryan procedure is very complicated and requires a sophisticated computer program for handling and analyzing data and that such programs are not widely available. Also, a comment stated that the procedure uses a relatively untried mathematical theorem and applies it in a fashion for which it was never intended. Another comment contended that the Mantel-Bryan procedure is "disturbing" in that, for certain sets of data, it is possible that different answers will be produced by different starting points in the computer interation, i.e., there may be an infinite number of possible answers. A comment stated that neither Mantel paper was published in a recognized statistical journal, and, therefore, that the papers have not been subjected to proper peer review. Another comment argued that the procedure is based on unwarranted assumptions. Other comments suggested that the procedure is too lenient, and several suggested use of the linear procedure for extrapolation. Finally, another comment recommended the use of the Hartley-Sielken procedure (Ref. 59) and contended that this procedure "has never been challenged."

In light of these comments, the Commissioner reexamined alternative statistical procedures for estimating

01191

test animal exposure levels that correspond to specified levels of risk. None of the procedures suggested in the comments is known to be entirely compatible with current knowledge about chemical carcinogenesis. The procedure chosen must be that best supported by current science and also most protective of the public health. Of the three general procedures recommended by the comments or available in the literature (the curvilinear models, linear extrapolation and the Mantel and Bryan procedure (Refs. 57 through 63)), the Commissioner has now decided that for purposes of this regulation, linear extrapolation best meets the above criteria:

(1) Of the available procedures, the linear procedure is least likely to underestimate risk. That is, at the level of acceptable risk (1 in 1 million over a lifetime), the maximum permissible dose of residues calculated by use of the linear extrapolation is usually lower than that obtained by the use of the other procedures.

(2) Linear extrapolation does not require the use of complicated mathematical procedures and can be carried out without the aid of complex computer programs. The Commissioner now agrees with those comments suggesting that the Mantel-Bryan procedure is, for such reasons, unsatisfactory. The curvilinear model of Hartley and Sielken (1977) and Crump et al. (1977), like the Mantel-Bryan procedure, have many computational difficulties and require data from several dose levels.

(3) No arbitrary selection of slope is required to carry out linear extrapolation. For this reason, the Commissioner believes that it possesses an operational advantage over the Mantel-Bryan procedure; again, the Commissioner agrees with those comments that pointed out this difficulty in the previously proposed procedure.

(4) an approach to risk estimation recently proposed by Cornfield (Ref. 64) has been suggested to the Commissioner. Although Cornfield's approach may have merit, its assumptions and concepts have not yet been sufficiently scrutinized, evaluated, and accepted for the agency to adopt it at this time, as illustrated by the recent dicussion in *Science* (Ref. 64).

(5) Finally, the Commissioner has accepted the recommendations contained in a report issued by an expert scientific committee of the Department of Health, Education, and Welfare (Ref. 63) Linear extrapolation was proposed as the procedure of choice by the members of this committee.

For the above reasons the Commissioner now proposes to adopt linear extrapolation for regulating compounds subject to these regulations. The Commissioner recognizes that alternative procedures may have merit. Accordingly, comments are solicited on the property of those alternative procedures and what is believed to be their advantages over the proposed linear procedure. Of particular interest is the applicability of the curvilinear procedures to an interpretation of data on time-to-tumor observations.

3. *Time-to-tumor and other considerations.* Serveral comments contended that the 1973 proposal was deficient because it did not address the time-to-tumor aspects of chemical carcinogenesis. Some comments pointed out that Albert and Altshuler have developed preliminary statistical relationships between low levels of carcinogen exposure and time of tumor manifestation (Ref. 65). These authors maintain that characterization of carcinogenic potential and potency on the basis of incidence alone is not appropriate because it ignores the life-shortening aspects of carcinogenesis. A comment of the same type was received in 1977.

The Commissioner generally agrees with these comments. He recognizes that he must consider all manifestations of chemically induced carcinogenesis, including decreases in latency times (life-shortening effects). Accordingly, the Commissioner has reviewed recent scientific publications that attempt to address comprehensively all manifestations of chemical carcinogenesis (Refs. 54, 59, and 65). These publications offer generalized statistical techniques purportedly suitable for estimating all types of risks from experimental animal data. As expected, they are complex in concept and demanding in skills required for use. Without prejudice toward the technical and scientific merits of these generalized techniques, the Commissioner proposes that the linear technique be adopted in these regulations. In the Commissioner's view, this simple-to-use technique can be adopted to deal with all manifestations of chemical carcinogenesis even though it was not originally elaborated with life-shortening effects in mind.

Simplicity of use, however, is only one aspect of the procedure that must be considered. Other important aspects are technical and scientific merits or deficiencies. Therefore, the Commissioner invites those interested and knowledgeable in statistical techniques for risk estimation to consider and comment on the scientific and technical merits or deficiencies not only of the procedure proposed but those of the curvilinear procedures as well. The Commissioner will review comments on the time-to-tumor issue and will make any appropriate modifications in the procedure finally adopted.

One comment in 1973 stated that "effects produced at higher dose levels * * * are useful for delineating the mechanism of action, but for any material and adverse effect, some dose level exists for man or animal below which adverse effects will not appear." The comment analyzed in detail the deficiencies of all statistical extrapolations and stated that approaches are available to define a true carcinogenic no-effect level. It contended that it is more appropriate to determine a biologically insignificant level using a safety factor based on competent scientific judgment. In 1977, several comments reiterated the threshold issue but provided no supporting information or justification. Further, one comment has claimed that threshold levels have been established for 23 chemical carcinogens, although it provided no data or information to support this assertion.

The Commissioner disagrees with the contention that the classical toxicology concepts of the terms "thresholds" and "biologically insignificant levels" are generally applicable to carcinogenesis. There is substantial scientific controversy over whether these concepts apply to irreversible processes, such as the chemical induction of malignant neoplasia. The concepts of "threshold" and "biologically insignificant level" derive from short-term toxicity experiments. They have no established meaning with respect to biological processes that require long latent periods (up to 20 or 30 years) before the manifestation of lesions.

If it could be shown that there exists a threshold level for carcinogenic effects below which no member of the exposed human population would be at risk of developing cancer, and if a method were available to establish such a level for specific carcinogens, the Commissioner would seriously consider adopting such a level as the no-residue standard for this regulation. There is reason to believe, however, that the classic toxicological concepts of "thresholds" and "biologically insignificant levels" may not apply to carcinogenesis, and, further, that even if they do apply, there is no known method for establishing them in a manner that will provide the public health protection necessary.

It is true that "no effect" levels have been observed for some carcinogens in bioassays conducted in experimental animals. Such observed "no effect" levels should not, however, be mistaken for "thresholds" or for "biologically insignificant levels." There are several reasons for this conclusion.

In the first place, animal experiments are limited in their power to detect carcinogenic effects. Most such bioassays test approximately only 100 animals at each dose level. If no response is observed in 100 test animals, the upper 99 percent confidence limit

01192

of the response is approximately 5 percent. Thus there is a probability that a dose level producing "no observed effect" in this type of bioassay actually produces a response up to 5 percent; such a response (cancer incidence) can by no means be considered insignificant, even for the small test animal population, let alone for the entire human population of the United States. Of course, an observed "no effect" level in a carcinogenesis bioassay may indeed represent a "true no effect" level for the test animal population; there is, however, no way to ascertain which of these two possible interpretations of observed "no effect" levels is correct.

Even if it were assumed that a "no observed effect" level derived from a carcinogenesis bioassay represented a "biologically insignificant" level for the test animal population, it is unclear how knowledge of such a level would permit establishment of a threshold level for an exposed human population. Animal studies are performed under carefully controlled conditions that allow as little variation as possible in the environments of treated and control groups. The test animals have a uniform diet, are generally of the same age and state of health, and are otherwise living under uniform conditions. Further, the animals usually used in experimentation are genetically homogeneous.

By contrast, the human population exhibits a broad range of dietary habits, health status, age, occupational environment and genetic background; such factors are known to influence responses to toxic substances. For this reason, the human population is expected to exhibit a far broader range of susceptibilities to carcinogens than does the small and relatively homogenous test animal population for which "no effect" data may be available. Some segments of the human population may be less susceptible to the effects of a carcinogen, and some more susceptible, than the test animal group (Ref. 74). There is no information available that permits a quantitative determination of the relative susceptibilities of test animal and human populations. Therefore, it is not possible to devise a "safety factor" that can be applied to the animal "no effect" level (even assuming such a level were biologically insignificant for the test animal) to arrive at a level that can be considered safe for the entire human population. Moreover, if the animal "no effect" level is biologically significant for the test animal population (and, as has been shown this is not likely), the use of such a level to assign a safe level of human exposure, even after application of their safety factor, could lead to dangerously high levels of risk for humans.

Although the available information regarding the relative susceptibilities of test animal and human populations does not permit a quantitative determination of relative susceptibility, there are comparisons of a limited number of carcinogens (Refs. 66, 67, and 75). These comparisons only indicate that the lifetime cancer incidence induced by exposures in man can be approximated by the lifetime incidence induced by similar exposures in laboratory animals and that man may be no more susceptible than the most sensitive test animals species for which test data are available.

In addition to the variety of difficulties associated with methods for assigning threshold levels, there is considerable uncertainty whether such thresholds actually exist. There is, for example, evidence that cancer can arise from a single transformed cell and that this transformation results from a single exposure and can occur long after the causative agent has been removed (Ref. 68).

The question of whether population thresholds exist for carcinogens is open for comment, and the Commissioner is willing to accept and take into consideration evidence that may develop on this issue. For the present, however, the Commissioner takes the position that there is no known method for establishing thresholds.

The Commissioner's view on this issue accords with that of an expert Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens contained in their Report to the Surgeon General, United States Public Health Service, April 22, 1970. The Report, which was published in full in "Chemicals and the Future of Man," Hearings before the Subcommittee on Executive Reorganization and Government Research of the Committee on Government Operations, United States Senate, April 6 and 7, 1971, contains the following conclusion:

> It is impossible to establish any absolutely safe level of exposure to a carcinogen for man. The concept of "toxicologically insignificant" levels (as advanced by the Food Protection Committee of the NAS/NRC in 1969), of dubious merit in any life science, has absolutely no validity in the field of carcinogenesis. Society must be willing to accept some finite risk as the price of using any carcinogenic material in whatever quantity. The best that science can do is to estimate the upper probable limit of that risk. For this reason, the concept of safe level for man, as applied to carcinogenic agents, should be replaced by that of a socially acceptable level of risk.

No information developed in the past 7 to 8 years warrants modification of this view.

Several comments opposing the proposal suggested that the agency should maintain flexibility and evaluate the approvability of sponsored compounds based on assessments of benfit and risk—in effect offering another approach to establishing the operational zero for carcinogenic residues. The Commissioner concludes, however, that an approach that contemplates considering the benefits of use of a sponsored compouund in defining the no-residue standard is incompatible with the anticancer provisions of the act.

It is the Commissioner's opinion, at least for new animal drugs, food additives, and color additives in animal feed, that it is improper to use risk/benefit considerations in making decisions about their safe use. The legislative history of the Food Additives Amendment of 1958 shows that the benefits of food additives are not to be considered in assessing whether they can be safely used. This position was strongly supported by the food industry. The industry feared that FDA would refuse to approve new, safe additives that provided only marginal benefits to the consumers or marginal improvements over additives already on the market (Ref. 69). Further, in that amendment Congress also added the flat proscription on the addition of animal carcinogens to the food supply. That action provides additional support for the position that (except for the very limited role assigned to the determination of functionality) risk is the only appropriate consideration in assessing safety under the food additive provisions of the act, which in large part governed the use of new animal drugs intended for use in food-producing animals from 1958 until the enactment of the Animal Drug Amendments in 1968.

As explained in Part I of this preamble, the legislative history of the Drug Amendments of 1962 shows that the DES proviso to the Delaney clause was added only to correct what Congress perceived to be an inequity in the regulatory system caused by FDA's application of the food additive provisions to the existing use of DES in cattle. But there is no basis for concluding that Congress by that action intended that an express risk/benefit consideration be added to the procedure for assessing the safety of substances intended for use in food-producing animals. Rather, Congress noted that the protection afforded the public would remain unchanged despite enactment of the proviso (see Part I.A.3 of this preamble).

The Animal Drug Amendments were enacted in 1968 to consolidate the various provisions of the act that were being used to regulate new animal drugs. The legislative history of that statute also contains no directive to FDA that the agency consider benefits in assessing the safety and approvabil-

01193

ity of a new animal drug. In the absence of explicit Congressional direction on this point, FDA historically has considered it inappropriate to balance the risk of cancer that may be associated with the use of a sponsored compound (and assumed by one societal group) against the benefits that may be derived from the compound's use (and accruing to a different societal group). Recent case law in United States Courts of Appeals for the 5th and the District of Columbia Circuit has addressed different situations (see *American Petroleum Institute* v. *OSHA*, 581 F.2d 493 (5th Cir. 1978); Petition for cert. pending No. 1036 (U.S. 1979); *Agna Slide 'N' Dive Corp.* v. *CPSC*, 569 F. 2d 831 (5th Cir. 1978); *Environmental Defense Fund et al.* v. *Environmental Protection Agency*, No. 77-1091 (D.C. Cir. Nov. 3, 1978); and *Hercules Inc., et al.* v. *Environmental Protection Agency*, No. 77-1248 (D.C. Cir. Nov. 3, 1978).

4. *Expression of dose level.* Several comments received before the February notice addressed the adjustments the Commissioner had proposed to make in the "safe" level derived from the experimental animal data in order to establish an appropriate value for man. Some comments stated that adjustments for differences in food intake between experimental animals and man were inappropriate when dealing with carcinogens. The comments stated that such adjustments would assume erroneously that all toxic materials have the some mode of action on a body weight basis. They further suggested expressing the relationship in terms of concentration in the feed of the test animals and in the food of man when the diet in both cases in consumed adlibitum, not on an amount-per-body-weight basis. Other comments argued that the extrapolation of animal data to man should be based on body-surface-area ratios.

The notice specified that carcinogenicity tests must be conducted with the test compound's concentration in the diet of the experimental animals held constant throughout the study. The safe or "acceptable" level derived from extrapolation of test animal data would be expressed as a concentration in the total diet (weight of compound/weight of total diet) of the animals and would be directly used as the acceptable level for the total diet of man. The Commissioner concluded that the arguments for conversion based on surface area ratios or on intake per unit of body weight have little basis. The comments provided no evidence that those concepts are applicable to low-dose chronic exposures. The concept of surface-area ratios is based on experience with short-term high-dose studies. Furthermore, measurements of surface area are crude. Finally, surface area and body weight will vary, as will food intake per day, throughout the chronic study, thus requiring constant adjustments of dose.

Until evidence is compiled demonstrating that there is a more appropriate means to extrapolate from experimental animal to man for chronic exposure and carcinogenic manifestation, the Commissioner will assume that the animal is the integrator throughout its lifetime of any observed response to a fixed concentration in the diet. The Commissioner has thus adopted the direct extrapolation approach (the safe level in parts per million, parts per billion, etc., of the diet of the experimental animals directly applied to the diet of man), which is appropriately conservative as well as the most practical of the approaches considered.

5. *Degree of data confidence.* The Commissioner disagrees with comments that characterized the proposal's requirement for 99 percent confidence intervals as another in a series of unnecessarily conservative assumptions. Confidence intervals characterize the quality of experimental measurement. The Commissioner maintains that a high degree of confidence should be demanded for decisions respecting carcinogens. The Commissioner therefore has adopted the 99 percent level of confidence, and the final regulations, reproposed herein, require that all calculations based on experimental observations be made from or with the 99 percent confidence limits.

6. *Slope used for extrapolation.* Because the Commissioner is proposing to adopt the linear model for risk estimation, comments on the slope used for the extrapolation are now irrelevant.

7. *Spontaneous tumor rates and data combination.* In the 1973 proposal the Commissioner recognized certain limiting features common to all extrapolation procedures, including that of Mantel and Bryan. These limitations concern the tumor incidence rate in the control groups of animal bioassays and the selection or combination of data from different experiments.

In response to comments, the Commissioner adopted in the February 1977 notice the procedure developed and utilized by Mantel et al. (1975) for handling spontaneous tumors. This procedure is an extension of the principles first articulated in the appendix to the 1961 Mantel paper and treats the rate of spontaneous tumors as an additional statistical parameter to be estimated from the data. The linear procedure in this proposal also treats spontaneous tumors in control animals as an additional statistical parameter to be estimated when two or more non-zero dose devels are utilized. When only one non-zero dose level is used for the linear extrapolation, an upper confidence limit on the increase in response of the dosed animals over the control animals is used. These methods of handling the data resolve some of the problems that arise when attempting to deal with spontaneous tumor rates.

Two comments in 1977 cautioned against the requirement for using the most "sensitive" test animals (i.e., the strain with the greatest tendency to develop tumors) as well as the "conservative" Mantel-Bryan procedure. They contended that these two requirements are incompatible because the high spontaneous tumor rate in the control animals reduces the number of animals that can manifest the effects of the chemical being tested.

The issue of sensitivity or susceptibility of the test animal species is relevant regardless of the statistical model selected for conducting the extrapolation. The commissioner does not intend to apply the term "sensitivity" or "susceptibility" in a way that is detrimental to the ability of the bioassay to detect carcinogenic potential, which has to be the overriding concern in selecting the test animal species.

In many instances, the male and female animals of the same strain may exhibit significantly different responses to a compound. Also, the responses of different strains and species may differ significantly. It is always desirable to make maximum use of available information by appropriately combining different data sets, but prudence must govern the process of selecting and combining data. Combining different data sets from the same or different experiments increases the number of animals used in the analysis and therefore increases the confidence in the results. Yet, in many instances, different data sets contain different types of information. Mantel et al. discuss the informational aspects of data combination for pooling data from different experiments and from different data sets in the same experiment. Although the Commissioner agreed in principle with most of their conclusions, it was nevertheless anticipated that situations would arise where the evidence in support of combining or not combining data would be equivocal. Therefore, the Commissioner concluded that the statistical and biological evaluation of data will determine which data sets, if any, will be appropriate for pooling. Where there are significant statistical and/or biological differences in the observed responses, only subsets of data representing statistically and biologically compatible bioassays will be combined for analysis.

01194

Further comments on this segment of the February notice alleged that the agency's criteria for combining data are vague, arbitrary, and always unnecessarily conservative. A comment stated that FDA always combines the data to produce the highest risk regardless of the rationale for that combination. Other comments contended that cancer is a disease of old age. For this reason, it was argued, animal tests should be conducted in a way that reduces interference in the relevant observations caused by the high spontaneous tumor rates expected in animals of advanced age. It was also argued that, for the purpose of selecting data for a risk analysis, the agency should disregard all benign tumors occurring late in the test animals' lives.

There are many examples in which carcinogenic response to a chemical insult is limited to a segment of exposed human or animal populations, e.g., a single sex. It is only reasonable, therefore, that bioassay data be evaluated for the presence of such specific responses, and that the results of these analyses determine the ultimate manner of pooling data. These ultimate analyses are neither artibrary nor vague and are based on well-established scientific principles. Further, they do not always lead to the "most conservative" interpretation of the data; these analyses attempt to identify the data base that will result in the closest approximation of the true risk. In the Commissioner's opinion, this process is not regulatory "overkill" by any means; rather, an examination of the process shows that each decision in the process is independent and must be made on the merits of the data available. The proposed methods for combining data are, in each case, reasonable and well accepted, and the end result of the process is also reasonable because of the independent nature of the individual steps. For example, the regulation stipulates that the appearance of either benign or malignant tumors or both is evidence of carcinogenicity. As numerous experts have noted, both types of tumors will ordinarily be taken into account for the purpose of estimating risk as long as they are dose-related. Both types of tumors represent a carcinogenic threat, and neither can properly be ignored (Ref. 12).

The occurrence of tumors late in the life of test animals is also evidence of carcinogenicity as long as tumors are dose-related and occur at a greater rate in the treated than in the control animals. The Commissioner has no basis to ignore, as one 1977 comment suggested, the occurrence of benign tumors that occur late in life.

The Commissioner believes that the correlation between the type and rate of occurrence of tumors in the test animals and in man is poorly known and that to ignore benign tumors merely because they occur late in the lives of test animals would be imprudent.

8. *Level of risk.* The 1973 proposal suggested that an acceptable level of risk for test animals, and thus for man, could be 1 in 100 million over a lifetime. Many comments argued that this level of risk was unnecessarily conservative in light of the many other cumulative, conservative restrictions already in the proposed regulations. In the February notice the Commissioner concluded that the 1 in 100 million level of risk was unduly limiting without substantial compensation in terms of public health. Consequently, the notice established the maximum risk to be used in the Mantel-Bryan calculation as 1 in 1 million. The Commissioner explained the basis for selecting that level. Although additional comments on the level of risks were expressly requested, the Commissioner received only two comments on this issue. They contended that the level of risk selected was inconsistent with the congressional intent in enacting the proviso to the Delaney clause and was insufficiently protective of the public health.

Because Congress specified that the use of carcinogenic animal drugs and feed additives should leave "no residue" to be found (by methods prescribed by the Secretary) in edible tissue, it appears that Congress intended that the use of such animal drugs and feed additives not significantly increase the human risk of cancer from that use. It is also evident, however, that Congress intended to permit the use of carcinogenic animal drugs and feed additives if there would be no significant increase in the human risk of cancer from that use. Historically, safety decisions involving the use of chemicals have been made with the aid of numerical safety factors that do not consider the actual level of risk to the public. Observed no-effect levels from animal data are divided by an absolute safety factor to give a "safe" level for humans. For carcinogens, the Commissioner has concluded that it is necessary for the agency squarely to face the level of risk associated with a chemical compound's use before the agency will permit the use, and it is for that reason the Commissioner is proposing the statistical procedure for assessing risks prescribed in this document.

In the Commissioner's opinion, the acceptable risk level should (1) not significantly increase the human cancer risk and (2), subject to that constaint, be as high as possible in order to permit the use of carcinogenic animal drugs and food additives as decreed by Congress. For the following reasons the Commissioner believes that a risk level of 1 in 1 million over a lifetime meets these criteria better than does any other that would differ significantly from it:

(a) The risk level of 1 in 1 million is an increased risk over the entire lifetime of a human being.

(b) The upper 99-percent limit on the response data is used throughout the procedure, and the extrapolation procedure is conservative by nature. For these reasons, the maximum concentration of residues of carcinogenic concern that will go undetected in edible tissues is expected to increase the lifetime risk of excess cancer in humans by less than 1 in 1 million.

(c) This 1 in 1 million *lifetime* risk is expected only if the maximum concentration of residues potentially undetected in edible tissues is consumed every day over a lifetime. Because there is little likelihood that these residues will be so consumed by humans, the actual risk is likely to be lower than 1 in 1 million.

(d) The use of the procedures explained in the proposed regulations for deriving a concentration of residues that may go undetected in edible tissues rests on the assumption that the only risk to the exposed human population is that from residues of the sponsored compound. Other causes of disease or death are not considered. Because the population is constantly at risk from a wide range of factors, any increment of risk associated with residues subject to this proposed regulation is in comparison with other risks, likely to be vanishingly small.

(e) Several other prudent procedures apply to the derivation of the concentration of residues that will be permitted to go undetected (see section V.D. of this preamble below). For these and the above reasons the most likely human risk is expected to be less than 1 in 1 million.

(f) Once the level of risk is as low as 1 in 1 million, any further reduction in the level would not significantly increase human protection from cancer.

(g) An increase in the level of risk to 1 in 10,000 might significantly increase human risk. It is difficult to choose between 1 in 1 million and 1 in 10,000 but the agency chose the more conservative number in the general interest of protecting human health.

Furthermore, considerable discussion of the issue of acceptable level of risk has taken place recently (Refs. 55, 70, 71, 72, and 73), suggestions for the acceptable level of risk range from 1 in 20,000 per lifetime to 1 in 100 million. In addition to protecting the public health and satisfying the congressional directive, the Commissioner believes the selected level of risk should be consistent with acceptable levels of

01195

risk for other materials that are considered safe, and should prevent any false sense of security in the calculations. After reviewing data on acceptable levels of risk and knowing the limitations on the procedures, the Commissioner has concluded that a level of risk of 1 in 1 million over a lifetime satisifies all of these criteria.

The Commissioner notes that for a few carcinogens, some limited comparisons have been made between risks estimated from animal experiments and those caluclated from human epidemiology studies (Ref. 66, 67, and 75). The tentative conclusion from these comparisons is that the lifetime cancer incidence induced by chronic exposures in man can be approximated by the lifetime incidence induced by similar exposures in laboratory animals. For this reason, the various conservative procedures and assumptions attached to the establishment of the permissible concentrations of potentially undetected carcinogenic residues should compensate for the possibility that for some carcinogens humans in general or some numerically significant groups of humans are more sensitive than test animals. Likewise, compensation must be made for the possibility of additive and multiplicative effects among the many carcinogens to which people are exposed daily. It is impossible to supply a quantitative estimate of the degree of compensation that results from the application of the various prudent procedures and assumptions. For these reasons the Commissioner has exercised caution by proposing an acceptable level of risk as low as 1 in 1 million.

In summary, the Commissioner has concluded that a risk level of 1 in 1 million over a lifetime imposes no additional risk of cancer to the public. A lower risk would not significantly increase the public health protection, but would probably proscribe the use of most animal drugs or feed additives. A risk level significantly higher than 1 in 1 million, for example 1 in 10,000, might present a significant additional risk of cancer to the public.

D. DERIVATION OF THE LEVEL OF TOTAL RESIDUES OF CARCINOGENIC CONCERN THAT CAN BE TAKEN AS SATISFYING THE NO-RESIDUE REQUIREMENT OF THE ACT.

As explained previously, a potential residue level corresponding to a lifetime risk of 1 in 1 million in test animals (i.e., the safe level derived from a statistical extrapolation procedure) can be considered the level that represents no significant carcinogenic burden in the total diet of man. This level was assigned the symbol "S_0" in the February 1977 notice, and expressed as a fraction in the total diet of the test animals, i.e., parts per billion, parts per trillion. The Commissioner concluded that it is the potential undetected residue level that is safe in the total diet of man.

In some cases, residues in addition to the sponsored compound itself will have been selected for carcinogenicity testing. In these instances, safe or acceptable levels will be derived for each of the compounds that has undergone testing. The compound exhibiting the lowest value for the safe level is the most potent carcinogen of those tested and poses the greatest potential carcinogenic threat among the residues. The Commissioner assumes that the smallest value of the safe levels of all the carcinogenic compounds tested represents the acceptable, total potential carcinogenic burden to man that may result from the administration of a sponsored compound to food-producing animals. This smallest value is assigned the symbol S_0. Because tested residues other than the one selected for S_0 may have exhibited carcinogenic properties (although less potent) and still other, untested residues may represent carcinogenic risks, the sum of the levels of all of the residues must be less than S_0 to ensure that any undetected residues do not present a significant risk of cancer to humans. Potential residues in the total human diet cannot exceed S_0 if that diet is to bear no significant carcinogenic risk to man as a result of the residues. The only residues that can be excluded from the sum or residue levels are those that have been unambiguously shown to be noncarcinogenic in accordance with the principles described earlier.

One comment stated that the Commissioner failed to provide a mechanism to ensure that the total residue (S_0) will be accurately measured in edible tissues.

The comment has misunderstood the construct of the regulations. The S_0 value is a projected acceptable total level of residue that is determined by calculations using bioassay (toxicology) data; it is not determined by totally individual analytical measurements. Therefore, the appropriate tasks with regard to safety are (1) determining the time when the total residues in edible tissue of target animals have depleted to S_0 and below, and (2) selecting a suitable marker compound to monitor total residues. The determination of the expected time of the depletion of the total residues to S_0 will be made in the second metabolism study, which is described in section VI below in this preamble. The second metabolism study will normally be conducted with radiotracer techniques that permit identification of a marker residue and target tissue. The regulatory assay will be used to monitor whether the total residue has depleted to S_0. The accuracy and precision of these techniques is well recognized and accepted.

E. CORRECTIONS FOR FOOD INTAKE

Several comments on the original proposal argued for, and others opposed, further adjustments based on patterns of food consumption. Some comments contended that the "safe" level of Mantel and Bryan in the animal diet should be directly applied as the upper allowable limit in man's diet and in any component food in the human diet. These comments argued that this limit should not be raised by considering the intermittency of consumption of particular foods or the proportion of the total diet represented by an individual food. They suggested that individuals who consume above average amounts of food would be exposed to above average, and thus possible harmful, levels of residues. Further, these comments contended that the act does not distinguish between the people who consume average diets and people who consume above average quantities of certain foods; the two groups are entitled to equal protection. They argued that adjustments for exposure frequency based on food consumption patterns assume that continuous long-term exposure to a carcinogen precedes the development of cancer.

Many other comments urged that adjustments be made based on the proportion of the specific food in the total diet and the frequency of exposure. These comments generally favored the use of food consumption data, so that the degree of conservatism would be more uniformly applied and would take into account the relationship of the particular food to the total diet.

The Commissioner disagreed with the contention that no adjustments should be made for factors of exposure. Section 512(d)(2)(A) of the act requires the Commissioner to consider the probable consumption of a drug and of any substance formed in or on food because of its use. All drugs, including carcinogens, are subject to the general safety provisions of the act. Consideration of the formation of chemical residues on food is necessary whether the drug is a carcinogen or a chemical toxicant of another type. There is no legal, scientific, or policy basis for concluding otherwise. The no-residue standard of the act has been defined as satisfied when the sum of the levels of all potential undetected residues of the sponsored compond (excluding only those that have been found to be noncarcinogenic) would not exceed S_0 in the total diet of man. Because products derived from food-producing animals do not constitute the total human diet, it is appro-

01196

priate that S_0 be corrected for probable human consumption of specific tissues. The Commissioner agreed, however, that any adjustments must be conservative to assure that all segments of the population are protected.

Muscle tissue and eggs can be considered, conservatively, to each constitute one-third of the total daily human diet. Because milk can constitute the total daily diet of some individuals (e.g., infants), the Commissioner concluded that no adjustment for this commodity is appropriate. Adjustments for frequency of exposure for tissues other than muscle, milk, or eggs, (i.e., kidney, liver, etc.) will be considered when data are available that permit the Commissioner to conclude that the average daily intake of residues will not exceed S_0.

The February 1977 notice used the symbol "S_m" to represent the level of total residues of carcinogenic concern that can be operationally defined as satisfying the no-residue requirement of the act for specific tissues. The S_m value represents the level of residues that is acceptable for specific classes of edible products that constitute finite percentages of the total diet. Because milk may constitute the entire diet of an infant, the S_m value is its S_0 value. But because muscle tissue constitutes one-third of the diet, the S_m value is 3 times the S_0 value of the compound.

One comment on this section of the regulations said that the Commissioner was opening an avenue to permit as much as 20 times the S_0 value in muscle tissue. This is emphatically not the case. The comment failed to recognize that the regulation establishes specific dietary conversion factors for muscle tissue, eggs, and milk (⅓, ⅓, 1, respectively), and conversions will be permitted for other tissues only when there are data to ensure that the S_0 will not be exceeded in the total diet.

One comment raised a question about the quality of data used to establish the dietary factors for the major tissues, but the Commissioner concludes that the factors are correct. Although there are indications that the American diet has changed considerably in some areas in the past few years (e.g., the consumption of fabricated foods), there is no evidence that the consumption of muscle tissue, milk, and eggs, which serve as the basis for the basic dietary factors, has changed.

F. OTHER POSSIBLE ADJUSTMENTS

Several 1973 comments urged that the regulation not provide for adjustments for the degradation of residues in food under normal conditions of storage and cooking. Other suggested that this data should not be required, but should be taken into account when available. Still other comments expressed the fear that this data would be used to dilute the conservative intent of the regulation; they argued that the term "normal condition of storage and cooking" would be difficult to define, and it might reduce protection in situations where actual storage and food preparation practices did not approximate experimental conditions. Finally, some comments suggested that these studies be required only when there is reason to believe that the information would assist in protecting public health.

One comment on the February 1977 notice averred that the agency proposed to permit food with illegal residues to be marketed on the theory that violative levels of residues would "dissolve" before the food could be consumed.

The Commissioner agreed that the criteria appropriate to these studies were not defined, and he deleted the references to postslaughter residue degradation studies from the February 1977 notice. When there is reason to believe that storage conditions or food preparation methods might lead to the formation of potentially toxic residue products, however, the Commissioner will require appropriate special investigations. Petitioners are encouraged to explore the postslaughter stability of residues. Experience has shown that residue stability can be a complicating factor in studies for validating assays for dosed tissues. The Commissioner encourages research in this area; but until appropriate information can be reliably incorporated into food safety decisions, these data will not be used to liberalize the regulatory requirements.

G. OTHER POSSIBLE SAFETY FACTORS

Originally, the Commissioner proposed that the calculated does be modified to account conservatively for drug use patterns, e.g., the administration of the drug in the treatment of diseased animals. Comments stated that disease incidence does not occur randomly within a geographic area or within specific animal groups. Although a disease may have an overall incidence of only 10 percent, the affected group may be located in a single area. Therefore, the Commissioner was unable to conclude that evidence exists, or other safety factors are available, to permit the agency to calculate the effect of such drug usage, and this provision was deleted. No later comments have been received on this point.

VI. METABOLIC STUDY TO SELECT MARKER RESIDUE AND TARGET TISSUE

A. THE CONCEPT

Before the use of a sponsored compound can be approved, the Commissioner must determine that a practical and reliable assay is available to measure carcinogenic residues at the level which discriminates safe from unsafe food, i.e., the assay must be capable of determining when S_m is exceeded in each edible tissue. One approach to this problem would be to require assays that can be used to measure every residue in each of the various edible tissues. Because the number of residues in edible tissues and the number of tissues can sometimes be large, it is unlikely that such an approach would be practical. There is another far more practicable approach, which sacrifices no principle of safety. This alternative approach centers on the concepts of a marker residue and a target tissue.

A market residue is a residue whose level in a particular tissue is in a known relationship to the level of the total residue of carcinogenic concern in all edible tissues and which, therefore, can be taken as a measure of the total residue of interest in he target animal. Once a marker residue is selected and its quantitative relationship to the total residue is determined, it is possible to calculate a level, for purposes of these regulations, R_m, which is that level of the marker residue that must not be exceeded in a selected tissue (the target tissue) if the total residue of carcinogenic concern in the edible tissues of the target animal is not to exceed S_m. The marker residue can be the sponsored compound or any of its metabolites, or a combination of residues for which a common assay can be developed.

The target tissue is that tissue in which the absence of the marker residue at R_m or above can be taken as confirmation that the safe residue level, S_m, is not exceeded in any of the edible tissues. When a marker residue and a target tissue are selected, a practicable assay must be developed that can reliably measure the marker residue in the target tissue at levels at least as low as R_m, and conditions of use of the sponsored compound must be established that assure that, in practice, the potential marker residue level in the target tissue does not exceed R_m.

When it is determined, using an assay demonstrated to be capable of reliably measuring the marker residue in the target tissue at levels at least as low as R_m, that there is no such residue at levels at or above R_m, it can be concluded that the no-residue standard of the act has been satisfied for all edible tissues in the animal under ex-

01197

amination. Conversely, if the marker residue is found in target tissue at levels equal to or greater than R_m, all edible tissues must be considered unsafe for human consumption.

B. APPLICATION: DATA COLLECTION AND CALCULATION OF R_m

1. *Marker residue.* Application of the concepts of marker residue and target tissue requires an experimental determination of the quantitative relationships of residues that might serve as marker residues (including any that have definitely been shown to be noncarcinogenic, because theoretically one of these might be selected as marker residue) to the total residue in each of the various edible tissues that might serve as target tissues. Further, because these relationships change with time, the levels of potential marker residues in the potential target tissues must be measured over time, and tissue concentration-time profiles must be constructed. These depletion profiles will be derived from measurements made in target animal tissues after cessation of exposure to the sponsored compound. Finally, because the results of carcinogenicity testing have been used to set limits for total potential undetected residues in each of the individual edible tissues, the depletion profiles must include measurements of the total residue in each potential target tissue to levels at least as low as the S_m appropriate to the tissue. Also, depletion profiles for one or more potential marker residues must be constructed and include measurements of levels of residues corresponding to the times when the total residue has reached S_m (Plates I and II set forth in proposed § 500.89).

Part III of this preamble describes the requirements for the study of the metabolic fate of a sponsored compound in target animals. Although the purpose of this earlier metabolic study is to provide information for selecting residues for carcinogenicity testing, the same principles and requirements are applicable here and must be followed in acquiring the information necessary to construct depletion profiles. However, to meet the depletion profile requirements prescribed by the regulations, a second metabolic study of the sponsored compound in the target animals may be necessary. This second and possibly more refined study may require using a larger number of animals. It will be necessary to determine the total number and the quantities of residues at several appropriate times, starting immediately after cessation of exposure and continuing until the residues in each of the potential target tissues have reached a level corresponding to a total residue level of the appropriate S_m for that tissue. If the initial metabolic study is done in a manner adequate to select a marker residue and a target tissue, of course, it need not be repeated.

Selection of a marker residue will be based on examination of depletion profiles. Generally, there will be a time at which the sum of the levels of the individual residues of carcinogenic concern will fall below the S_m appropriate to the tissue under examination. Residues that are potential markers will be present at a known concentration (R_m) at this same time (Plate I), and in a definite (although perhaps rapidly changing) quantitative relationship to the total residue (Plate II).

With the quantitative relationships established, it will be possible to select one of the residues as a marker. Ordinarily, the residue selected will have the following characteristics: (i) It will represent at least 10 percent, and usually more, of the total residue burden at the time the total residue was depleted to S_m; (ii) it will be stable, easily isolated and characterized, and susceptible to manipulation for assay development and implementation; and (iii) it will be undergoing relatively rapid change in concentration at the time the total residue burden is at or near S_m (i.e., a change in its concentration will be a sensitive indicator of the time when the total residue burden has depleted below S_m). Although other considerations may enter into the selection of a marker residue, these three will ordinarily be most important.

There may be instances in which no single residue can adequately fulfill the requirements a marker residue must meet. In such instances, it may be necessary to select some combination of residues which, taken together, can represent the total residue burden. It should be noted that a marker residue can be a compound which is not a carcinogen, but is an unambiguous indicator, in the manner already described, of the presence or absence of carcinogenic residues.

2. *Target tissue.* Selecting a target tissue requires a comparison of the depletion profiles for each of the edible tissues (Plate I set forth in proposed § 500.89). A target tissue will be selected on the basis of assurance that the absence of the market residue at or above R_m means that carcinogenic residues are absent from the tissue that requires the longest time to achieve its S_m, and thus that the entire animal is free of carcinogenic residues.

When a compound is to be used in milk- or egg-producing animals, milk and eggs will be target tissues in addition to one tissue selected as the target tissue to represent the depletion of residues in all of the edible carcass. In these cases, it may be necessary to select a marker residue for milk or eggs that is different from the marker residue selected for the target tissue representing the edible carcass.

3. *Calculation of R_m.* The R_m for a marker residue is the level of that marker residue which is present in the target tissue at the time, T_L, when the sum of the levels of the residues in the tissue that requires the longest time to achieve its S_m (excluding any residues that have definitely been shown to be noncarcinogenic) is equal to S_m for that tissue. The depletion profiles will be used to select R_m (Plate II set forth in proposed § 500.89).

For example, assume (i) that liver is the target tissue of animal drug, P, intended for use in cattle; (ii) that the only residues of P are the parent compound, P, and a metabolite, P_{101}; (iii) that T_L is 3; (iv) that S_m for the sponsored compound is 29 parts per billion; and (v) that the following is a chart of the depletion profile of the drug.

Time	Total residue burden	P	P_1
0	100.00	75.0	25.0
1	65.4	41.6	21.8
2	42.0	25.3	17.3
3	29.0	15.0	14.0
4	21.0	9.0	12.0
5	15.0	5.0	10.0

In this case, before the drug can be approved for use, the petitioner must develop an assay that will satisfy the evaluation criteria in liver for either P at least as low as 15 parts per billion or P_1 at least as low as 14 parts per billion. Because P is depleting faster than P_1, when the total residue burden is 29 parts per billion, P may be the preferred compound to select as the market residue because it provides a more sensitive assessment of when the total residue burden reaches 29 parts per billion (S_m). Another example is provided in Plate II in proposed § 500.89.

Comments on the marker residue-target tissue segment of the regulations posed questions about the definition of terms and the implementation of procedures. One comment requested that the Commissioner add a table of definitions for the entire subpart, and it suggested that the agency coin a new term for the "marker residues." Another comment questioned whether the studies required to identify the marker residue and target tissue are truly "metabolism" studies. The February 1977 notice stated that the Commissioner would select the target tissue and marker residue, and one comment suggested that they be selected by the petitioner, who has a better knowledge of both the sponsored compound and of the availability of technology to develop assays for metabolities. Another comment questioned whether the agency is requesting sufficient information on edible

01198

tissues to permit a determination of a marker residue or target tissue. It also questioned why the most slowly depleting tissue is not always the target tissue. It further requested that the target tissue concept be clarified when a target animal is used for milk or egg production.

The terms "marker residue" and "target tissue" are defined in proposed § 500.83, and their meanings will be codified by the final regulations. For clarity, a new section is added to define all new terms for the subpart. The term "metabolic study" has been used by FDA to describe the types of studies called for by the regulations for many years. The Commissioner disagrees that the term is inappropriate.

The Commissioner agrees that the petitioner for a sponsored compound has a role in selecting the marker residue and target tissue. Under current agency procedures, the selections are made with the opportunity for participation by the petitioner, and thus the petitioner's knowledge and proponent status are recognized. Because the agency must make the decision on whether the sponsored compound can be safely used, however, it must remain the ultimate decisionmaker.

The regulations require petitioners to determine the tissue depletion profiles for residues, and for a sponsored compound a considerable part of this information will already have been gathered by the initial metabolism study. (See section III of the preamble.) The Commissioner concludes that it is appropriate to select the target tissue from among tissues likely to become storage depots or to be involved in metabolism and excretion of the sponsored compound. Routinely examining other more specialized tissues in great detail will yield little additional useful information. Material balance calculations will be used as necessary to determine whether other tissues are potential storage depots and therefore may be target tissues.

The criteria for selecting the marker residue and target tissue are such that, when the marker residue concentration passes through its R_m in the target tissue, all other residues in the tissues, including the most slowly depleting tissues, will have passed through their R_m. Therefore, the most slowly depleting tissue need not be the target tissue.

Finally, the Commissioner explained in the February notice that for milk- and egg-producing animals, it is necessary to have a target tissue in addition to the milk or eggs. To clarify this matter, the Commissioner added this requirement to the regulations.

VII. Sponsored Compounds Affecting Pools of Carcinogenic or Potentially Carcinogenic Substances Endogenous To Target Animals

A. Applicability of No-Residue Requirement

The act requires that in making food safety decisions, the Commissioner take into account all substances formed in or on food by the administration of sponsored compounds to food-producing animals. It is well recognized that: (i) Several substances endogenous to food-producing animals are suspect or proven carcinogens (Ref. 64); (ii) in any given animal species or breed, the size of pools of such endogenous substances may vary widely and are affected by such factors as sex, age, lactation, state of estrus, pregnancy, and geographic location; and (iii) humans have had sustained exposure to such endogenous substances for centuries. Whether normal levels of human exposure to these substances are responsible for human carcinogenesis is unknown, but using drugs that can cause an increase in human exposure to these compounds has the potential of increasing the risk of human carcinogenesis. Under the act, therefore, the use of such drugs must be controlled.

In dealing with potentially carcinogenic endogenous compounds, the 1973 proposal declared that the intent of the no-residue requirement of the act is the maintenance of the normal human dietary content. Thus, the February 1977 notice required the determination of the effects of sponsored compounds on the normal background levels of potentially carcinogenic endogenous compounds. If a compound is found to increase these levels, conditions of use are to be established so that normal background levels are not exceeded in the animal when the animal is slaughtered. The notice also required development of practical assays for measuring levels of endogenous compounds.

Several comments on this segment of the 1973 proposal expressed concern over the meaning of the term "endogenous compounds" and questioned how these compounds are to be distinguished from "exogenous compounds." Others questioned whether the former term includes chemical derivatives (estradiol benzoate) of bona fide endogenous compounds (estradiol) or essential nutrients (some amino acids, minerals, vitamins). Comments also expressed doubt about the distinction between endogenous and exogenous compounds when the administered compound can be metabolized to residues of both classes. Some comments also argued that all externally administered compounds should be considered exogenous, as the true meaning of the term implies.

Other comments suggested that endogenous substances of interest be subjected to toxicological testing and tolerances be set if such substances are found to be not carcinogenic. Some doubted that available technology could meet the proposed requirements. They contended that the terms "normal conditions of use" and "normal background levels of endogenous compounds" would be either extremely difficult or impossible to define. While recognizing the difficulty of the task, the Commissioner concluded that administered compounds that increase the naturally occurring level of potentially carcinogenic endogenous compounds present special problems of control, which the proposed regulations had to address and resolve.

As the Commissioner explained in the February 1977 notice, an endogenous compound is any compound that is metabolically produced by and is present in untreated target animals. Any sponsored compound which, when administered to a target animal, is found to increase the normal background levels of a potentially carcinogenic endogenous compound is subject to these proposed regulations, regardless of how the increase is brought about. For instance, estradiol benzoate, which by the above definition clearly is not an endogenous compound, is metabolically converted to the endogenous compound estradiol and may thus cause an increase in normal background levels of that substance. Estradiol may itself be administered and possibly cause target animal pools of estradiol to increase above background. Finally, a sponsored compound may indirectly cause an increase in tissue levels of estradiol by affecting any number of hormonal regulatory systems in the target animals.

Although in each of the above-cited cases the cause of the increases in normal background levels of estradiol is different, the result is the same. And it is the result that must be monitored and controlled. It is thus of little use to distinguish between "endogenous" and "exogenous" administered compounds. Rather, it is useful only to distinguish between administered compounds that can cause changes in normal background levels of potentially carcinogenic endogenous compounds and those administered compounds that do not affect such levels.

Essential nutrients are not included in the definition of the classes of compounds that will be regulated by these proposed regulations. In a strict sense, essential nutrients are not endogenous. Although present in the tissues of animals and required for growth

01199

and health, they are not produced by the animals and must be supplied from external sources. These features place essential nutrients in a distinct class of "required exogenous compounds," which must continue to be regulated in a unique manner. Determination of the allowable use of essential nutrients must reflect the target animals' nutritional requirements. When used according to label directions, supplements of essential nutrients that present carcinogenic risks should restore, but must not exceed, the essential nutrient levels found in natural foods adequately sustaining normal growth of healthy animals. Furthermore, the levels of such essential animal nutrients found in human food derived from animals with diets supplemented with essential nutrients must not exceed the levels in food derived from normal healthy animals fed a nutritionally adequate natural diet.

B. GENERAL PROCEDURES

If available information shows that a sponsored compound might affect pools of potentially carcinogenic endogenous substances above the level considered to be safe under the criteria of these proposed regulations, the petitioner would be required to investigate whether such effects occur under the conditions of the compound's proposed use.

The Commissioner proposes the following requirements: (i) Establishment of normal background levels (or "norm") of the endogenous compound of carcinogenic concern in the target animals; (ii) determination of the effects of the sponsored compound on the norm; (iii) establishment of safe conditions of use of the sponsored compound by demonstrating how the compound can be used in a way that ensures that the norm is restored in the target animals before slaughter; and (iv) development and validation of a practical assay to measure the endogenous compound at levels specified by the norm. The proposed regulations specify how each of these steps is to be accomplished.

C. SPECIFIC STEPS REQUIRED

The petitioner would first be required to determine experimentally the normal background levels, or norms, of the potentially carcinogenic endogenous compounds of concern in untreated target animals. A norm must be specific for the untreated target animals. The petitioner would provide the norm in the form of a cumulative frequency distribution of the observed levels of the endogenous compound. This curve must also include 99 percent confidence limits (Plate III appearing in proposed § 500.89).

The median and shape of the frequency distribution must be known so that shifts in the norm can be measured. For this reason, the assay used to determine a norm must yield values for the endogenous compound different from zero for at least two-thirds of the untreated target animals. This latter requirement is a compromise between the need to determine the frequency distribution with a high degree of reliability and at the same time to recognize the difficulties thay may be encountered in measuring levels at the lower end of the norm.

The petitioner would then determine the effects of the sponsored compound on the norm and provide data on the postexposure decay of any observed increases in the norm. The norm is considered restored when the distribution of values for the endogenous substance of concern observed in a group of treated animals is, with 99 percent confidence, the same as the norm.

The norm, as defined, takes into account those variables that affect background levels. The proposed regulations thus resolve the difficulties raised by 1973 comments suggesting that "normal background levels" would be difficult to define.

D. ENDOGENOUS MARKER RESIDUE: CALCULATION OF R_m

If the norm of an endogenous substance of carcinogenic concern can be increased by the administration of a sponsored compound, the endogenous substance can become an endogenous marker residue, i.e., its presence above certain levels can be considered an indicator of potentially carcinogenic residues in food. Approval of the use of such a sponsored compound is contingent upon the petitioner's furnishing of data demonstrating that the norms are restored in the target animals before slaughter, and upon the availability of a practical assay that can reliably measure the endogenous marker residue in target animals. This regulatory assay must be capable of measuring the marker residue at the level, R_m, corresponding to the 33d percentile of the norm (Plate III set forth in proposed § 500.89).

The R_m for an endogenous marker residue derives from a conceptual approach entirely different from that used for the derivation of an R_m for an exogenous marker residue. To monitor shifts in the norm, the Commissioner must be able to measure the median and to determine the shape of the distribution. An assay capable of measuring the 33d percentile of the norm provides the analytical capability necessary to determine whether the norm has been shifted by administering the sponsored compound to the target animals because it permits measuring two-thirds of the points on the distribution curve. The same assay evaluation criteria apply to endogenous compounds as to other compounds covered by these proposed regulations.

Accordingly, the commissioner in the February 1977 notice revised the provisions which, as proposed, would have originally established the lowest limit of reliable measurement at the 99th percentile of the norm. As the comments noted, as assay that can measure only the upper 99th percentile would not be able to detect any shifts in the norm, which is its primary function. The proposed regulations require an assay capable of a lowest limit of reliable measurement of the 33d percentile of the norm, which will readily detect any shifts in the median or mean of the norm. Determination of compliance depends on a regulatory system that monitors shifts in the norms and not levels of endogenous substances in individual animals.

E. ALTERNATIVE PROCEDURE

Earlier comments contended that an alternative to the foregoing procedure should be available for regulating endogenous substances. It was suggested that a tolerance for an endogenous compound can be established at levels above the norm, provided that appropriate toxicity testing on the compound is carried out and a safe level can be established in accordance with sections IV through VI of this preamble and proposed §§ 500.84 through 50090.

Separate mechanisms with distinctly different rationales have been developed to measure compliance with the no-residue standard of the act for endogenous and exogenous compounds. As noted earlier, for exogenous compounds, the regulations would require development of an assay with a lowest limit of reliable measurement at or below the level needed to ensure that any undetected residues pose essentially no increased risk of cancer in the population. On the other hand, the method for measuring compliance with the no-residue standard for an endogenous substance is based on the norm.

In the absence of toxicology data of the type needed to determine a safe level for exogenous compounds, described in section V of this preamble, the Commissioner maintains that restoring the norm is the only way to ensure the absence of unaccepatble risks resulting from the use of compounds that may increase pools of potentially carcinogenic endogenous substances. If the toxicology data are available, however, and are suitable for extrapolation by the procedures described in section V of this preamble, the Commissioner will permit a shift in the norm equal to the incre-

01200

ment shown to produce a lifetime cancer risk no greater than 1 in 1 million.

The 1977 notice announced that the Commissioner was receptive to suggestions for other alternative mechanisms of control. Two comments argued that the Commissioner has no authority to regulate increases in potentially carcinogenic endogenous substances that occur "indirectly" from the administration of the sponsored compound. They contended that the Commissioner can only regulate substances that derive directly from the sponsored compound, not from its use. The Commissioner rejects these comments, which are analogous to the earlier comments that the agency can regulate only a parent compound, not metabolites, under the Delaney clause. As explained in the February 1977 notice, the Commissioner is concerned about the use of compounds that may increase the pools of potentially dangerous endogenous substances that may be formed in or on food because of a sponsored compound's use. The general safety provisons of the act clearly cover all substances formed in or on food due to the use of a sponsored compound, and it is proper to consider excess levels of endogenous compounds of carcinogenic concern as such substances.

A comment requested that the Commissioner specify which potentially carcinogenic endogenous compounds are within the purview of this section. The Commissioner concludes that the proposed regulation covers all endogenous compounds that animal or human data show may present a carcinogenic risk.

Concerning the comment that all endogenous substances should be proscribed from use in animals, the Commissioner advises that there is no legal basis for their outright prohibition. Furthermore, the regulations prescribe procedures for use of these substances that ensure the same degree of safety as that required for the use of exogenous compounds.

Finally, a comment stated that the studies described in the February 1977 notice are costly, and it contended that, unless the data collected are considered proprietary, the requirement puts pioneers in the field at a disadvantage. The comment also requested that the Commissioner specify the studies required to define the norm and measure its restoration.

Under the current law, the Commissioner concludes that data on the norm are safety data required for every application and are proprietary data for new animal drugs. However, to reduce unnecessary testing, expenses to the regulated industry, and costs to the government, it is the agency's policy to encourage joint funding of tests.

The Commissioner believes it inappropriate to establish, as part of the regulations, detailed protocols for studies required to establish norms. However, the following example is offered as a guideline. To determine, with a high degree of confidence (99 percent), the characteristics of the distribution of the individual values that constitute the norm, the petitioner will ordinarily be required to examine a reasonable number of animals in each production class of target animals in which the sponsored compound is proposed for use, both treated and untreated. In each group, 450 to 500 animals will be sufficient to determine with 99 percent confidence:

(1) That the 99th percentile of the norm is less than the largest observed value; and

(2) That the cumulative frequency distributions of the observed levels of the endogenous compound in untreated target animals and in the treated target animals do not differ by more than .10 at any specific point.

To test whether the norm for the sample of untreated animals and the values for the sample of treated animals came from the same population, i.e., there was no effect due to treatment with the drug, the petitioner may use the Kolmogorov-Smirnov two-sample test. This test is concerned with the agreement between two cumulative frequency distributions. This test is sensitive to any type of difference in the distributions from which the two samples (treated and untreated) were taken, e.g., differences in location (mean, median, etc.), differences in variation, differences in skewness, etc.

The only assumptions required for this test are—

(1) That the samples are random samples;

(2) That the two samples are mutually independent; and

(3) That the samples are from a continuous population.

Specifically, the Kolmogorov-Smirnov test evaluates the probability of the maximum absolute difference that would occur between two cumulative distributions if they were obtained from the same population. For the details of conducting the test see Refs. 77 and 78. It must also be remembered that the above-described study may be conducted in lieu of chronic toxicity tests, and it can be conducted during the effectiveness studies. Thus the costs of developing and marketing an endogenous compound will be comparable to the corresponding costs for an exogenous compound.

VIII. Regulatory Assay: Evaluation Criteria and Approval Process

A. Introduction

The Commissioner can approve a sponsored compound for use in food-producing animals only if the intended use of the compound does not result in the accumulation of potentially carcinogenic residues in edible tissues and if an assay is available that can reliably measure such residues at and above the R_m. The assay must also be suitable for monitoring food from animals administered the compound to prevent food from reaching the marketplace if it is adulterated with potentially carcinogenic residues resulting from misuse of the compound.

Many comments in response to the 1973 notice contended that more explicit criteria and evaluation procedures should be specified.

The Commissioner agrees with these comments. Because the assays required by these proposed regulations are to be used for regulatory monitoring of residues of potential carcinogenic concern in food, rigorous criteria must be established for approval of these assays. Furthermore, the proposed assay must be subjected to an objective evaluation to determine whether it meets the criteria. Only then can there be assurance that an assay will provide a reliable and practical monitoring device to prevent violated residues in food. Most of the questions raised in the comments arose because the 1973 notice contained only a brief description of the assay evaluation criteria and procedures. Accordingly, the following discussion sets forth, as in the 1977 notice, the evaluation criteria and their bases.

Any assay used for regulatory purposes is characterized by a set of attributes that determine its quality: dependability, practicability, specificity, accuracy, and precision. These regulations specify objective criteria for these attributes. A proposed assay must be shown to meet these criteria during studies in a single laboratory and also in interlaboratory studies in government regulatory laboratories. The latter requirement is essential because the assays are to be used in Federal regulatory laboratories (FDA, USDA) and State laboratories, and the Commissioner must determine in advance that an assay will perform satisfactorily in more than one such laboratory. The proposed regulations specify that the interlaboratory validation study must be carried out in those laboratories (USDA and FDA) that will be using the method in surveillance and enforcement programs.

The steps in obtaining approval of an assay are—(1) assay development and study by the petitioner to deter-

01201

mine whether the assay satisfies the acceptability criteria; (ii) FDA review of the petitioner's study to determine suitability of the assay for evaluation in interlaboratory study; and (iii) interlaboratory validation study, again with approval contingent upon satisfaction of acceptability criteria.

B. SOURCES OF DATA TO SUPPORT THE ASSAY

Data from studies of an assay using three types of samples are necessary to support approval. The petitioner must prepare and analyze samples of target tissue to which known and varying concentrations of marker residue, including R_m and concentrations above and below R_m, are added ("spiked" tissues). The petitioner must also compare responses obtained from assays using these tissues with responses obtained from assays of target tissues known to be free of marker residues (control tissues). In plotting observed instrumental response versus concentration of marker residue, i.e., in constructing the analytical curve from these data, as many samples as possible should be run, preferably by different analysts, because interlaboratory validation of the assay will eventually be required. The variability among different analysts can be determined at the developmental stage and adjustments made before the assay is submitted for FDA review.

Before submitting an assay to FDA for review, a sponsor should be satisfied that it meets all of the evaluation criteria and also that it is consistent with general principles of good analytical practice. Past experience shows that a petitioner's failure to follow good analytical practices during initial assay studies often results in interlaboratory failure even though the initial results may appear satisfactory during a paper review of the assay by FDA. A petitioner should assure that no results enter the construction of an analytical curve when it is known that the results were obtained using other than acceptable principles of analytical practice.

In addition to the spiked tissue tests, a petitioner must also submit data showing the applicability of the proposed assay to target tissues taken from target animals treated with the sponsored compound ("dosed" tissues). Validation of the assay requires dosed tissue samples that contain the marker residue at a level approximating R_m. The petitioner is required also to submit a standard analytical curve constructed by taking the marker residue of known purity at different concentrations, determining the response, and plotting the relationship.

C. SUBMISSION OF DATA

Agency resources for reviewing and validating assays are limited. The Commissioner therefore would establish in this proposal a precise format for submitting the data to support acceptance of an assay. It is a well-recognized principle, applied both by the courts and administrative agencies, that a standard format can be required for pleadings, requests for licenses, and other applications. This format may also designate special types of information that must be contained in the submission. Therefore, the agency would refuse to accept a petition or review an assay when the request for approval fails to conform to the format outlined below.

1. *Assay description and petitioner's evaluation.* The petitioner must provide a complete description of the assay to allow FDA to determine whether it is potentially acceptable. Because this threshold determination of acceptability will trigger an extensive interlaboratory validation procedure, the discussion must be sufficiently rigorous to minimize waste of agency resources. Therefore, the submission must discuss in detail—

(a) What equipment and reagents are necessary;

(b) How the assay is performed; and

(c) How the assay complies with the criteria of dependability, practicability, specificity, accuracy, and lowest limit of reliable measurement prescribed in proposed § 500.90(d) and discussed under section VIII. E. below in this preamble.

2. *Data.* The data and worksheets, including spectrograms, chromatograms, etc., from the spiked tissue, dosed tissue, and control tissue analyses and the external standard and quality control data are also necessary for the preliminary review of the assay to determine whether it actually complies with the evaluation criteria.

D. FDA REVIEW

The agency will conduct a paper review of a petitioner's submission to determine whether an assay complies with the acceptability criteria. These regulations generally alert potential petitioners to the applicable statutory standards and criteria, which should permit a petitioner to assess preliminarily the acceptability of an assay before filing a petition, and thereby reduce the agency's workload.

If on preliminary review an assay appears to comply with the evaluation criteria, it will then be subjected to the interlaboratory assay validation study to determine whether it is indeed a practicable and reliable regulatory tool. Should the initial review establish the assay fails to meet these criteria, the petition will be denied. A conclusion that an interlaboratory assay validation study should be initiated, however, in no way guarantees that a proposed assay will eventually be approved.

The assay criteria and attributes set out in the proposed regulations represent and amalgamation of statutory and scientific standards. Because a variety of terms are in use, the Commissioner is proposing to adopt and define the basic terms in the regulations in simple language for the sake of clarity. Accordingly, an assay must meet the following attributes and criteria for approval:

1. *Dependability.* Dependability is the likelihood that the proposed assay will not fail to yield a result because of uncontrollable features inherent in its design. Almost all assays will, on occasion, fail to yield any result. Often this failure occurs due to mishandling by the analyst, but sometimes failure may be the result of some aspect of the assay itself that may have been inadequately studied and defined or that cannot be controlled. For example, assays depends upon the availability of a standard against which measurements are compared. If the integrity of the standard depends on certian environmental factors (e.g., purity of the solvent in which it is maintained, temperature, light intensity, etc.) and these factors are understood, it may be possible to prevent assay failure. If this dependence is not know, however, the assay may fail and may fail often depending on the effect of the environmental factor of importance on stability of the standard. In this example, failure can mean a highly inaccurate result, assuming some fraction of the standard's intergrity is retained, or it can mean no result at all, assuming complete loss of integrity.

Assays used to monitor carcinogenic residues in food must be free of such uncontrollable features. Failure of a proposed assay to yield results during the petitioner's assay development studies or interlaboratory validation study can be a ground for refusing to accept the assay and for denying the underlying petition. Accordingly, the regulations require a petitioner to furnish information on, and provide an explanation of, runs of the assay that are begun, but never finished, during the analyses of samples used to construct the submitted analytical curve.

2. *Practicability.* Proposed § 500.90(d)(2) defines the practicability attribute as follows:

The assay is considered practicable only if it is suitable for routine use in a government regulatory laboratory. The time required to complete the assay must be consistent with regulatory objectives, monitoring, compliance, etc. All supplies, equipment, reagents, standards, and other materials necessary to conduct the assay must be either commercially available, or readily available from the petitioner, on request. The Commission-

01202

er will withdraw approval of any assay and initiate regulatory action against the sponsored compound if such a condition of the compound's approval is no longer satisfied.

The Commissioner has established criteria for practicability in terms that relate specifically to the nature of the laboratories in which the assay will be used, i.e., regulatory laboratories where the time and availability of equipment and reagents are critical factors in their ability to perform satisfactorily the mandate functions.

The inability to use an assay at a regulatory laboratory because a needed reagent is not readily available or because excessive time is requred to complete the assay presents potential risks to publish health and, therefore, precludes approval of the assay. Obviously, some assays will require some unique items, particularly reference standards. The Commissoner agrees with comments suggesting that, as long as a sponsor makes reference standards available to all persons having an interest, this requirement of the regulation will be met. A commitment to supply reference standards when they are not commercially available may be made a condition of the sponsored compound's approval, and failure to supply the governmental or other laboratories as required is a basis for withdrawing a compound's approval. The Commissioner concludes that an assay is not practical if it is dependent on the use of any other unique equipment or materials that are not commercially available.

3. *Specifity.* The regulations provide that, for an assay to be accepted, and observed response must be due to the compound that is being measured, and to that compound only. It is a fundamental part of the development of an assay to determine whether or not it possesses this important attribute. Among analytical chemists and biochemists, an "assay" that does not demonstrate this attribute is of little value; and indeed, in a regulatory setting, such an assay could be dangerously misleading. For this reason, the Commissioner has established rigorous specifications for this attribute.

In general terms, "specificity" refers to the uniqueness of the relationship between the observed effect (or response) and the applied stimulus (in this case the chemical under analysis). In analytical chemistry and biochemistry, the term "specificity" is commonly used to refer to the uniqueness of a response resulting from the application of a stimulus having specific characteristics; that is, the term has a qualitative dimension only in that it does not relate to either the quality of response or stimulus or to the nature of the relationship between response and stimulus. Both of the latter criteria, which might also be considered aspects of specificity, are central to good analytical practices. The regulations consider both the qualitative and quantitative aspects and groups them together under the general attribute of "specificity." The Commissioner's objective is to assure that, whatever the observed response, it is uniquely related to the marker residue both qualitatively and quantitatively.

The establishment of an analytical curve (not simple a standard curve, but one derived from actual measurements obtained on tissue samples containing known amounts of marker residue at different levels and from control samples) provides the means to detemine whether the responses produced by an assay are single-valued, as they must be if an assay is to be considered fully specific. Only assays that yield continuously increasing or decreasing analytical curves will satisfy the criterion of single-valuedness. The criterion of single-valuedness, or montonicity, must be established for the full range of possible contamination of residues, i.e., from zero residue levels up to levels of residues that will be present if no withdrawal period is observed.

The regulations require that the assay contain a sufficient number of independent measurements utilizing independent physicochemical principles to assure specificity (i.e., the identity of the marker residue must be confirmed). There are many ways in which specificity can be demonstrated experimentally. A petitioner may use highly sophisticated research tools to demonstrate that a proposed assay is specific in the ways discussed above. However, a regulatory analyst, using an approved assay, must have available some technique that can provide assurance that an observed response is due to the market residue. At present, although there are other possibilities, mass spectrometry is probably an ideal choice for acquiring the requisite specificity. Some determinations (e.g., those requiring enzymes) may have an inherent high specificity, but others have low specificity (e.g., gas, thin-layer, and liquid chromatography) and require other independent types of measurements to achive the requiste confirmation of identity. The requirement in the regulations that an assay contain a sufficient number of independent measurements negates the effect of a false positive measurement.

4. *Accuracy.* Assays yield measurements of concentration that are in some proportion to the true concentration of the compound being measured. The ratio of the measured to the true concentration of the compound, expressed as a percentage, is a measure of the assay's accuracy. The accuracy of an assay is determined from data collected from two types of studies.

One type of study must yield graphs of the observed concentrations of the marker residues, as determined by analysis, plotted against the corresponding levels of marker residue added to the analyzed target tissue. The plot is to be used to ascertain whether the assay meets the above-specified criteria.

The other type of study must measure the assay's recovery of marker residue from target tissue of target animals exposed to the sponsored compound. If target animals exposed to a radiolabeled sponored compound produce radiolabeled marker residue, it will always be possible to measure the proposed assay's recovery by directly comparing measurements obtained from the proposed assay and appropriate measurements of radioactivity. If it is not possible to have radiolabeled marker residue, the true concentration of marker residue in target tissue from exposed animals must be determined by exhaustive extraction of such tissues after appropriate standard treatments which hydrolytic enzymes.

The regulations prescribe specific accuracy criteria The average of observed responses must be between 60 and 110 percent of the true level of the marker residue when the lowest limit of reliable measurement, L_m, which is described in the next paragraph, is less than 100 parts per billion and between 80 and 100 percent of the true value if L_m is equal to or greater than 100 parts per billion. These criteria need not be satified throughout the full range of the analytical curve, but they must be satified in the range from L_m to three times L_m. These criteria are consonant with current good analytical practice.

5. *Lowest limit of reliable measurement (L_m).* To be accepted for regulatory purposes, an assay must be able to distinguish, with a high degree of confidence, target tissues that contain levels of the marker residue at or above R_m from target tissues that do not. This distinction must be reproducible and capable of supporting legal action when violative residues of the sponsored compound occur.

To provide the necessary degree of discrimination, the regulations require that the assay be capable of producing when the marker residue is present in target tissue at or above R_m a response that is, with 99 percent confidence, different from the response in nontreated (control) target tissue, i.e., the difference between the responses of control target tissue and target tissue containing the marker residue at or above R_m is, with 99 percent confidence, greater than zero.

The actual lowest limit of reliable measurement for the proposed assay is termed the "L_m", and it will be determined by reference to the analytical

01203

curve of the proposed assay. The L_m will be the level of marker residue that gives a response above the expected blank value that is greater than, or equal to, 0.75 times the spread of the 99 percent confidence limits of a single assay response measured parallel to the observed assay response axis (see Plate IV in proposed § 500.90(d)(5)).

If the determined lowest limit of reliable measurement, L_m, of the proposed assay is equal to or less than the R_m, this criterion will be considered satisfied. This procedure takes into account the attribute of precision. Thus, an assay that satisfies this criterion will provide a reliable regulatory tool to enable the Commissioner to discriminate safe from unsafe food.

The Commissioner recognizes that the term "method sensitivity" is widely used to describe the lowest level of a compound under analysis that can be detected and measured with an analytical assay. Indeed, the original proposal used this term to describe what is now termed "the lowest limit of reliable measurement." However, there is some confusion surrounding the term "sensitivity." It derives in part from the fact that the term has been used in two senses: (1) As the lowest level of a compound that can be detected by an assay; and (2) as the lowest level of a compound that can be measured reliably by an assay. In fact, the correct meaning of the term "method sensitivity" is unrelated to a particular level of compound concentration, but rather relates to the ratio of change in instrument response to the change in compound concentration. The term "sensitivity" has therefore been dropped from this proposal. The Commissioner has adopted the term "lowest level of reliable measurement" because that term more accurately describes the attribute.

In response to comments urging that any "detected residue" should be subject to regulatory control, the Commissioner points out that it is an inherent characteristic of almost all analytical methods that componds can sometimes be detected at levels below the levels at which they can be reliably measured. More precisely, detection of a compound simply means that there is some instrument response above background levels that could be the compound of interest, but this response cannot be considered a reliable measurement or identification of the compound (Ref. 9). Since public protection is the goal, the Commissioner must be in a position to document conclusions based on analytical data, often in a court of law. A major aim of these proposed regulations is to assure that assays used to obtain such data can reliably measure residues. Hence, the Commissioner concludes that the discriminant for samples containing potentially violative exogenous marker residues must be the lowest limit of reliable measurement, L_m, of the approved assay.

Several comments on the 1977 notice stated that the definition of L_m and the procedures for determining L_m were incompletely specified. Most comments applauded the Commissioner's attempts to specify analytical attributes and agreed that the criteria were in accord with current good analytical practice. Several comments suggested that further specification of the interagency validation procedure might be desirable, and thus offered assistance if detailed guidelines were to be drafted in the future.

The Commissioner agrees with these comments and is proposing to define L_m in detail in the regulation as described above.

There was some confusion regarding the definition of "accuracy," and one comment stated that the regulations confused the terms "accuracy" and "recovery." The Commissioner agrees that in the February notice the term "accuracy" is used in a manner equivalent to what is normally termed "recovery." The term "accuracy," however, is more in line with analytical chemistry terminology, and the differences between accuracy and recovery occur only when dealing with absolute analytical methods, which will not be of concern here. For these reasons the Commissioner is proposing to retain the term "accuracy."

E. INTERLABORATORY VALIDATIONS OF ASSAY

Although FDA will review the assays for each sponsored compound, the actual regulatory field examination of foods of animal origin will be primarily performed by USDA under the Meat and Poultry Products Inspection Acts, and by the States under the Public Health Service Act. The Food and Drug Aministration performs a complementary regulatory function: Followup analytical and field investigations of violative residues to assemble evidence for use in regulatory actions.

The initial paper review by FDA of material in a petition permits the agency to make initial determination of the acceptability of an assay. Adequate protection of the public health, however, requires assurance that these assays will function in the government's regulatory laboratories. Therefore, these regulations also prescribe the procedure that will be used to assure that an assay is appropriate for use as as regulatory tool by government laboratories.

The Commissioner is proposing to require that three government laboratories (two FDA facilities and one USDA facility) independently validate an assay before it can be determined that use of a sponsored compound can be approved. This requirement is necessary because of the delicate nature of the assays, their importance in assuring that no residues of carcinogenic concern will occur in food of animal origin, and the practical limitations on the government's capacity to monitor food production and distribution. These three laboratories must study an assay sufficiently to assure that all criteria are met and that the petitioner has drawn correct conclusions in the submission about the assay's acceptability.

A comment on the 1977 notice suggested that FDA adopt the Association of Analytical Chemists' procedure for validating the assays. At this time, the Commissioner believes the AOAC process is inappropriate. It is very time consuming and permits testing in laboratories other those of FDA or USDA, where the assay will be used as a regulatory tool. Because of the delicate nature of the assays covered by these regulations and the time periods imposed for evaluating applications, the Commissioner declines to adopt the AOAC procedure. When the agency gains experience with the assays, however, the Commissioner will reconsider adopting in the regulations the AOAC assay validation process.

F. CONCLUSION

If an assay complies with the criteria described above and prescribed by the proposed regulations, and compliance can be verified under actual conditions of regulatory use (see section IX of this preamble), the Commissioner will approve the assay. A full description of the approved assay will be published in the FEDERAL REGISTER upon approval of the petition, in accordance with the provisos to the anticancer clauses and section 512(i) of the act.

IX. WITHDRAWAL PERIODS

A. INTRODUCTION

The regulations propose to define the withdrawal period for a sponsored compound as the time required, after cessation of target animal exposure to the sponsored compound, for the marker residue to deplete to L_m in the target tissue. The withdrawal period must also be compatible with actual conditions of livestock management and reasonably certain to be followed in practice. Because of the way in which the regulations define "marker residue," "target tissue," and "L_m," the use of a sponsored compound in accordance with the prescribed withdrawal period will assure that no carcinogenic residues of the compound will be present in human food derived from treated animals. At any point after cessation of exposure but before

01204

the determined withdrawal period, treated animal tissues must be considered as containing residues of carcinogenic concern. Thus, the withdrawal period specifies the length of time after the last treatment with a sponsored compound in which animals must not be slaughtered for food and during which milk or eggs must be discarded.

Several comments on the 1973 proposal addressed the procedures for establishing post treatment withdrawal periods. Some contended that the requirement for tissue equilibration (no change in concentration of residues in the tissue with change in time) with residues in the experimental procedure for establishing withdrawal times was inappropriate for therapeutic drugs. Other comments suggested that the withdrawal periods be established to assure the absence of residues from edible tissues only, because they are the ones destined for human consumption. Some of these comments expressed concern about the practicality of applying confidence-interval techniques to establishing withdrawal periods, especially when dealing with large animals. Finally, one comment requested clarification on whether confidence limits or tolerance limits were to be used in setting withdrawal periods. The following paragraphs contain the Commissioner's response.

B. DATA TO SUPPORT WITHDRAWAL PERIODS

The depletion studies required by the proposed regulations to establish withdrawal periods must take into account the biological variability among animals and other vairables, e.g., assay variability, that may influence depletion times.

Residue depletion studies must be conducted under conditions of the sponsored compound's maximum proposed use. If a sponsor can demonstrate target tissue equilibration with the marker residue, however, a shorter period of administration than the maximum dose for the longest proposed conditions of use will be permitted. The conditions of the study must also simulate actual use conditions. The commissioner agrees that a compound intended for therapeutic use need only be administered according to the compound's maximum conditions of proposed use. The proposed regulatory assay must be used to measure the marker residue in the target tissue, including milk and eggs where appropriate, because it is this assay that will be used for regulatory monitoring.

All relevant data and evaluations must be submitted with the petition, along with a graphical presentation of the tissue depletion curve (concentration of marker residue in target tissue versus time).

The analysis of the data must include the estimated depletion curve, which in most instances may be adequately approximated by a first-order decay process. The statistical tolerance limit for the 99th percentile will be determined for the samples from individual target animals, and the time of intersection of this limit with the L_m value will be determined. The withdrawal period is the interval of time between the last administration of the compound and the time of intersection of this statistical tolerance limit on the observations and the L_m of the approved regulatory assay, plus an additional interval determined by rounding out this time interval to provide a practical withdrawal period compatible with animal management practices (Ref. 79).

For example, if the time of intersection of the statistical tolerance limit for the 99th percentile on the individual tissue determinations and the L_m for the marker residue is 39 hours, the withdrawal period (preslaughter interval) would be established as 2 days. In the case of milk samples, if the time of intersection were 63 hours, a withdrawal time of 72 hours (discard of six milkings) would be established.

The use of a compound will not be approved if the necessary withdrawal period is incompatible with animal management practices. For example, the use of a compound in lactating animals will not be approved if the required withdrawal time for milk exceeds 96 hours (4 days) because the management practices of milk production make observance of such discard times unlikely, or at least not reasonably certain, to be followed in practice.

When the marker residue is an endogenous compound, the withdrawal period is the time after cessation of administration of the sponsored compound required for the norm to be restored (see sections VII., C, D, and E above) and extended if necessary to be compatible with conditions of livestock management. The validated regulatory assay must be used to collect this information.

C. RATIONALE FOR USING THE STATISTICAL TOLERANCE LIMITS APPROACH

To establish that carcinogenic residues are absent from edible tissues of food-producing animals treated with the sponsored compound, the Commissioner must have information about the rate of residue depletion and the inherent metabolic variabilities among individual target animals.

The Commissioner is proposing to use statistical tolerance limits for this section to provide the degree of confidence (99 percent) necessary to ensure protection of the public health. Confidence limits, as used elsewhere in this regulation, estimate population parameters (e.g., 99 percent confidence limits will result in an interval that contains the true response rate 99 times out of 100). Statistical tolerance limits, however, are used to provide a specified degree of confidence that a specified portion of a population is below a given value (e.g., 99 percent confidence that, if the withdrawal period is followed, 99 percent of the target tissues will contain residue levels below L_m).

One comment on the February notice argued that withdrawal periods are unenforceable and contrary to the normal practices of the meat industry.

Section 512(d)(2)(D) of the act (21 U.S.C. 360b(d)(2)(D)) provides expressly that, in determining whether a compound is approvable, the Commissioner is to consider whether the conditions of use of a sponsored compound are reasonably certain to be followed in practice. Historically, safe conditions of use have included a preslaughter withdrawal period for many compounds intended for food-producing animals, and the compound's labeling requires that this period be discussed. In the Commissioner's opinion, withdrawal periods are being followed for most compounds, although some violation will always occur. However, one of the primary functions of this regulation is to improve the procedure for setting withdrawal periods and thereby provide FDA with stronger tools for enforcing compliance with withdrawal periods and for taking regulatory action if violative residues are detected.

Three comments raised questions about the use of the term "99 percent confidence interval." Another comment suggested that using the 99 percent confidence limits on the data in calculating the withdrawal period is too conservative and will result in unduly long withdrawal periods.

To clarify, the Commissioner has defined the term "99 percent confidence interval" in the proposed definition section. The Commissioner does not agree that the proposed approach is "too conservative." By using the statistical tolerance limit on the data, the Commissioner ensures with 99 percent confidence that in 100 sampled tissues there is no more than one violative residue when the labeled withdrawal period is followed. Minimizing the likelihood that a violative residue will occur is an important public health objective, and the Commissioner maintains that the procedures provided in these regulations (the use of a validated assay to collect residue data under proposed conditions of use; the use of statistical tolerance limits to establish withdrawal periods; and the use of good animal husbandry practice to aid

01205

in determining whether withdrawal periods will actually be followed) provide the proper balance in setting a withdrawal period that ensures that (1) the food consumed, if the withdrawal period is followed, will be safe, (2) the withdrawal period is in accord with good animal husbandry practice and will be followed, and (3) violations can and will be detected.

Two comments raised questions about collecting data with the validated assay in the tissue depletion studies to determine the withdrawal period. Because assays are not validated until the final stages of a petition's review, the comments stated that it is impossible to collect data to establish a withdrawal period with the validated assay.

The Commissioner disagrees. For reasons already stated, the withdrawal period must be established with the assay for which approval is sought. Further, collecting the data by any method not proposed for validation imposes a repetitive administrative burden on the agency that is costly and unwarranted. When the data are collected with a different assay, the agency must first assess the quality of the data-collection assay and the appropriateness of the data submitted. Then it must attempt to compare the data-collection assay with the one proposed for validation. In the Commissioner's opinion this simply is an unacceptable waste of limited government resources; therefore, the Commissioner rejects any suggestion that the withdrawal period be established using an assay that is not submitted for validation.

A comment on withdrawal periods for endogenous substances contended that it is unnecessary to show when the norm is restored. The comment argued that merely showing that the norm is restored is adequate, regardless of when the restoration takes place. The Commissioner disagrees because the rate of the norm's restoration is an important consideration in setting the withdrawal period. It determines when food derived from treated target animals will be safe for human consumption. Only with such information can the necessary withdrawal periods be established.

Finally, two comments found unclear the statement that sponsors shall submit all raw data collected in determining withdrawal periods. They suggested that the regulation be reworded to require submission of all appropriate supporting data. The Commissioner agrees and intends to require submission only of all data that are relevant to determining withdrawal periods. Relevant data include, for example, descriptions of all assays on specific tissues, worksheets, and calculations, as well as daily calibration data (i.e., standard curves, spiked tissue, and background values).

X. Compliance

When a target tissue is examined with the approved assay and is found to contain the marker residue at or above its L_m, the Commissioner will conclude that the carcass from which the target tissue was taken contains carcinogenic residues and, therefore, that the sponsored compound has been used in violation of the act.

When target animals are found to contain an endogenous marker residue at or above the 99th percentile of the norm (Plate III in proposed § 500.89(c)(1)(ii)), they will be designated as potentially violative. Because there is at least a 1-percent probability that untreated target animals will contain endogenous marker residue above the 99th percentile of the norm, further investigation will be necessary to determine whether the sponsored compound has been used in violation of the act. The function of this investigation will be to determine whether the potentially violative sample originated from target animals whose median level of the endogenous marker residue is greater than the median of the norm (and hence, the need for a regulatory assay having an L_m at the 33d percentile of the norm). The proposed regulation also requires that, before regulatory action is begun, it must be determined whether or not the approved compound was used to treat the target animals under investigation.

Guarding against any shifts in the norms should allay all fears expressed in comments that monitoring only at the 99th percentile, as proposed, would not permit detection of any general increase in human exposure to potentially carcinogenic endogenous substances.

Food containing residues of any approved sponsored compound that has been used in accordance with the conditions of the compound's approval is specifically excluded from the adulteration provisions of section 402(a)1) of the act by sections 409(a), 512(k), and 706(a). Thus, administration of the sponsored compound according to the approved labeling is a defense to any criminal action that might arise for a violation of section 402(a)(1) of the act. However, within the meaning of section 402(a)(2) of the act, such food is adulterated if it contains a residue of the approved sponsored compound which is unsafe within the meaning of sections 409, 512, and 706. A residue is unsafe under those sections when it occurs in food at levels above those approved for use, and any residue found at levels equal to or above the L_m is unapproved and therefore illegal. To establish that the residue is unsafe (an adulterant) within the meaning of sections 409 and 512 of the act, the agency must establish that the detected residue actually is a residue of the sponsored compound; and when the agency can prove this point, it has proved that the food is adulterated as a matter of law.

The proposed regulation requires each assay to meet specific criteria before the Commissioner will approve the sponsored compound or use, and an assay satisfying these criteria will permit the agency to discriminate between target tissue background responses and responses due to the marker residue. Levels of residues that are below the L_m value cannot be distinguished from background with confidence, and the results of these findings are inadequate to support a regulatory action. On the other hand, when marker residues are detected and measured at or above L_m with the approved regulatory assay, this finding will unquestionably support regulatory action since it constitutes evidence that the food is adulterated within the meaning of section 402(a)(2) of the act. (See *United States v. Ewing Bros. Co., Inc.*, 502 F.2d 715, 725-726 (7th Cir. 1974), cert. denied 420 U.S. 945 (1975).) Moreover, a finding of a violative residue will warrant further administrative action because it will constitute a prima facie case that the compound has not been used in accordance with its conditions of approval, and the agency will conduct a further investigation to determine what additional regulatory action, if any, is appropriate.

XI. Waiver of Requirements

The proposal would permit the Commissioner, in response to a petitioner's request or on the Commissioner's own initiative, to waive, in whole or in part, any of the foregoing requirements for the scientific evaluation of sponsored compounds that have the potential to contaminate human food with residues whose consumption could engender a human risk of carcinogenesis. It has long been settled that an agency may adopt a rule shown to be appropriate for the generality of instances and leave the correction of injustices to applications by those concerned (e.g., *National Nutritional Foods Ass'n v. Food and Drug Administration*, 504 F.2d 761, 784 (2d Cir. 1974) cert. denied 420 U.S. 946 (1975)). For these reasons, the Commissioner has expressly included the waiver provision. The Commissioner advises, however, that a waiver will be granted only in exceptional circumstances, and, as the regulation provides, the basis for any waiver must be documented.

01206