Bruce Weiskotten

What plans, if any, does the DOE have for identifying and managing PFAS, microplastics and the more than 600 chemicals approved by the FDA for which we have no laboratory assay? How does the DOE plan to monitor and manage such chemicals when we have no ability to detect them? Does the DOE have any case studies of the effects of PFAS or GRAS (Generally Recognized As Safe) chemicals on fish, amphibians and shellfish? Does DOE have any way to monitor levels of such GRAS chemicals in surface water?

ENVIRONMENTAL DEFENSE FUND, BREAST CANCER PREVENTION PARTNERS, CENTER FOR ENVIRONMENTAL HEALTH, CENTER FOR FOOD SAFETY, CONSUMER FEDERATION OF AMERICA, CONSUMER REPORTS, DEFEND OUR HEALTH, ENVIRONMENTAL WORKING GROUP, GREEN SCIENCE POLICY INSTITUTE, HEALTHY BABIES BRIGHT FUTURES, LEAGUE OF CONSERVATION VOTERS

June 3, 2021

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Citizens petition requesting that the agency take more aggressive action to protect consumers from per- and poly-fluoroalkyl substances (PFAS) by banning all forms that biopersist in the human body

Dear Commissioner:

The United States is awash with per- and poly-fluoroalkyl substances (PFAS). Their widespread use and their ability to remain intact in the environment means that over time PFAS levels from past and current uses can result in increasing levels of environmental contamination, and accumulation of certain PFAS has also been shown in humans and animals.[1] Thousands of these substances have been used across various industries and goods,[2] including in firefighting foam,[3] food packaging,[4] and household products.[5] People are exposed to PFAS from products we use, the food we eat, the air we breathe, and the water we drink, especially in communities near where the chemicals are produced, processed, used or disposed. As a result, PFAS have been measured in the bodies of virtually every person that has been tested in the US[6] and in thousands of drinking water sources.[7] The Biden-Harris Campaign's Environmental Justice Plan identified tackling PFAS contamination as one of the new administration's top priorities.[8]

The scientific evidence showing widespread harm to health, especially to children, from the most studied forms of PFAS is overwhelming.[9,10,11] And, the more PFAS are studied, the more we learn that substances misleadingly touted by the chemical industry as safer forms of PFAS[12] are linked to harm and contamination.[13,14,15] The cumulative effect of PFAS from all these sources on our health, including our risk of cancer, harm to our immune system and impaired development of our children, has resulted in a national outcry for comprehensive action; states have been compelled to take action because the federal government's piecemeal approach has left residents at risk.[16,17,18,19]

The Food and Drug Administration (FDA) has been a significant contributor to the consumer's exposure based on past approvals, but the extent of the food contamination from the substances the agency currently allows is largely unknown because the agency does not test for them. It wasn't until 2012 – long after the Environmental Protection Agency (EPA) began to act – that the FDA first took steps, albeit incomplete, to remove long-chain PFAS from food packaging.[20,21] However, FDA continued authorizing food contact substances (FCSs) made from short-chain PFAS and treating them as a safer alternative despite the lack of information[22] on their potential biopersistence, toxicity and cancer risk. Only in 2020 did the agency begin a five-year process to phase out some short-chain PFAS[23] after the chemicals' manufacturers balked at conducting the cancer, reproductive, and developmental toxicology studies that FDA said were necessary to determine whether the uses might be safe.[24]

Adding to these failures, the agency continued to authorize FCSs made from other types of PFAS even though it knew those substances had also not been adequately studied. As recently as April 2021, FDA's

scientists published a study reviewing the toxicology of ether-PFAS that acknowledges little is known about their ability to biopersist in the human body and that these materials have major toxicity data gaps.[25] Studies recently made public indicate that a PFAS-ether compound used to manufacture food packaging outside the US has a half-live similar to PFOA and PFOS.[26]

FDA has a duty to take broader and more aggressive action under the Federal Food Drug and Cosmetic Act (FFDCA) to ensure food is safe. The law demands that no use of PFAS – or any other food contact substance – be allowed unless there is "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" after considering three factors including "[t]he cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet."[27]

Therefore, we now petition the agency to protect consumers from further harm by banning all long- and short-chain PFAS as FCSs and systematically reassessing its past actions based on a presumption that all per and poly-fluorinated compounds (PFCs) biopersist in the human body unless there is affirmative evidence to the contrary. PFC is a broad term that FDA has used previously and comprises not just those chemicals with alkyl chains but also other forms including cyclic chemicals. Based on this presumption, FDA should take aggressive action to protect consumers from all PFCs.

A. FDA regulation of PFAS as food contact substances

The FDA has designated short-chain and long-chain PFAS as two distinct classes of chemically-related substances.[28] For each class, the agency has determined that there is sufficient evidence that one or more members are absorbed by the gut, are distributed in the blood, and accumulate in the human body ("biopersist"); likewise, for each class there is a lack of toxicology studies necessary to demonstrate safety. Therefore, the chemicals within these classes and FCS that contain or release these chemicals into food cannot be considered safe.

For the long-chain PFAS (LC-PFAS) class, in 2008 FDA treated them as a class due to their biopersistence, carcinogenicity, and reproductive and developmental toxicity and identified seven FCS notifications (FCNs) for substances that the agency classified as members of this class. In response, the manufacturers of those PFAS agreed to phase out their use in food in 2011.[29] Today, the seven FCNs remain effective with a flag stating that they have been "voluntarily ceased by the manufacturer." This status is not recognized by the FFDCA or the agency's regulations and is not binding on food manufacturers; FDA essentially put the substances in a limbo. In 2016, in response to a food additive petition by several of those joining on this petition, the agency revoked its prior regulatory approvals of other LC-PFAS due to similar safety concerns but took no action on the seven FCNs that still remain in limbo.

For the short-chain PFAS (SC-PFAS) class, on October 1, 2019, FDA sent letters to three companies that have effective FCNs for these substances.[30] In the letters, the agency stated that a member of the class known as 6:2 fluorotelomer alcohol (6:2 FTOH) biopersists in the body. FDA said that because biopersistence increases the internal dose, additional, long-term cancer, reproductive, and developmental toxicology studies were needed to demonstrate safety of 6:2 FTOH monomer and associated low molecular weight oligomers, with specific evaluation of impacts on the immune system, nervous system, and reproductive tract after birth. Without this evidence, all members of the SC-PFAS class should be considered unsafe consistent with the precedent set by FDA in its 2016 decision on LC-PFAS and with 21 C.F.R. § 170.18.

Through FDA's December 2020 response to a Freedom of Information Act (FOIA) request by the Environmental Defense Fund and Environmental Working Group, we learned that the agency:

- Rejected one company's offer to conduct the necessary studies because the time to perform them (at least two years) "would take too long to complete", in an attempt to accelerate the market removal of these chemicals in light of the risk posed by their biopersistence;[31] and
- Accepted, without apparent negotiation, a unified offer made by the companies to a five-year phase-out of their products for food use. This is a clear contradiction to the urgency it conveyed to the one company that two years was too long to wait for studies.

The phase-out plan FDA agreed to is described on the agency's webpage[32] as follows:

- "Beginning in January 2021, three manufacturers will begin a 3-year phase-out of their sales of certain substances that contain 6:2 FTOH for use as food contact substances in the U.S. marketplace.
- After the phase-out period, it is anticipated that it may take up to 18 months to exhaust existing stocks of paper and paperboard products containing these food contact substances from the market."

The agency added that it will monitor "the progress of the phase-out of these short-chain grease-proofing agents through annual updates provided by the three remaining manufacturers." It did not indicate how it will approach any deviation from the proposed plan.

Despite the determination that FDA lacks sufficient information to demonstrate the safety of SC-PFAS, FDA has taken no apparent action on FCSs in the class other than those associated with 6:2 FTOH. In addition, other forms of PFAS and PFCs that do not fit the LC- and SC-PFAS classes remain authorized by FDA.

Despite its past flawed assessments of the risks posed by LC- and SC-PFAS, we have seen no indication that FDA has systematically reviewed its approvals and authorization for all PFCs including PFAS, polymers and oligomers, to determine whether there is sufficient evidence of safety in light of the new information. In addition, the agency has taken no action to prohibit companies from determining that uses of these substances are generally recognized as safe (GRAS). Because FDA allows companies to make these safety determinations in secret without notifying the agency, it would have no way to ensuring that PFAS and PFCs are not used as FCSs without banning all forms of PFCs, including all PFAS in regulations.

B. Action requested

We specifically request that FDA comply with the FFDCA and its implementing regulations by:

- Revoking the effectiveness of all FCNs that contain a member of either the LC-PFAS or the SC-PFAS classes as an ingredient, manufacturing byproduct, impurity, breakdown product or metabolite pursuant to 21 C.F.R. § 170.105;
- Evaluating its food additive or GRAS regulations at 21 C.F.R. Parts 172 to 188 and removing any approvals that contain a member of either the LC or SC-PFAS classes;
- Issuing a regulation in 21 C.F.R. Part 189 banning use of SC-PFAS and LC-PFAS in food contact materials whether packaging or food handling equipment; and
- Requiring that industry provide sufficient information to affirmatively demonstrate that all PFCs, including all PFAS that are not in the SC-PFAS or LC-PFAS classes, their impurities, byproducts, and metabolites do not biopersist or may cause cancer by non-genomic means in order for their continued use in food contact materials to remain authorized. If the evidence is not

provided, then FDA should remove all approvals and authorizations. In case FDA determines that their uses are safe, the companies must submit an environmental assessment evaluating the impacts from production, processing, use, recycling, and disposal of these substances per the National Environmental Policy Act.

C. Statement of grounds

The FDA is responsible for ensuring food is safe.[33] For food additives and food contact substances, safety means there is "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" after considering three factors including "[t]he cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet."[34] Despite determining that there is sufficient evidence that the use of LC-PFAS and SC-PFAS are no longer safe due to biopersistence and toxicity, the agency has taken only limited action and that action falls short of its responsibilities under FFDCA.

In the analysis below we provide a detailed explanation of the grounds on which FDA should take the requested action.

1. FDA has designated SC- and LC-PFAS as two distinct classes of chemically-related substances.

2. For each of the PFAS classes, the agency has determined that there is sufficient evidence that one or more members of the class biopersist, and that the available toxicology data is inadequate to establish safety, and therefore, the use of any member in the class cannot be considered safe.

3. Despite acknowledging that LC- and SC-PFAS classes are not considered safe, FDA improperly allows food contact materials containing members of those classes to remain in use.

4. The agency's failure to anticipate that these two classes of PFAS are biopersistent and carcinogenic when it authorized their use underscores the need for FDA to reassess other PFCs, including PFAS, as the agency's initial assessments for these substances may be similarly flawed.

We explore each of these findings in more detail below.

B.1 FDA has designated SC- and LC-PFAS as two distinct classes of chemically-related substances.

B.1.1 FDA has designated LC-PFAS as a class of chemically-related substances.

In its January 4, 2016 rulemaking, FDA removed its prior approval of three LC-PFAS[35] to repel oil and water in paper and paperboard contacting aqueous and fatty foods because it concluded there was "no longer a reasonable certainty of no harm for the food contact use of these FCSs."[36] In essence, the agency found the use of these FCSs was no longer safe as that term is defined in 21 C.F.R. § 171.3(i).

The agency reached this conclusion because it found that the three FCSs were members of a class of LC-PFAS (a type of long-chain perfluorinated compounds (long-chain PFCs))[37] that were not safe. Specifically, FDA stated that:

> As a result of this review, we concluded that data for subsets of long-chain PFCs (demonstrating biopersistence and reproductive and developmental toxicity) are applicable to long-chain PFCs on a general basis and that this data raises significant questions as to the safety of the authorized uses of the three FCSs subject to the petition.[38]

FDA defined the class as having "extended alkyl chains where all of the hydrogens are replaced by fluorine (hence the FCSs are "perfluorinated")" with the "perfluorinated alkyl chains greater than or equal to eight carbons in length . . ."[39] In other words, LC-PFAS are substances with alkyl chains of eight or more carbons with all of the hydrogens on those carbons replaced with fluorine.

B.1.2 FDA designated SC-PFAS as a class of chemically-related substances.

In a 2020 letter to Daikin,[40] FDA states, in part:

> Recently available toxicological data on 2-(perfluorohexyl)ethyl alcohol (CAS Reg. No. 647-42-7) (6:2 fluorotelomer alcohol (FTOH)), one of the impurities listed for the FCS in FCN 1493, reveals concerns for biopersistence of a key metabolite, 2H, 2H, 3H, H-perfluorooctanoic acid (5:3 acid) (CAS Reg. No. 914637-49-3).

These chemicals, 6:2 FTOH and 5:3 acid, fit the definition of "short-chain per- or polyfluorinated substances (short-chain PFAS)" as defined by FDA in footnote 1 of the same letter. The footnote says "'Short-chain PFAS' refers to PFAS with seven or fewer carbons in an alkyl chain (n-1 carbons are perfluorinated)."[41]

In addressing Daikin's products, FDA said:

> The subject FCS in FCNs 820, 827, 888, 933, 1044, 1360, and 1451 are intended for use as grease-proofing agents to be applied to paper and paperboard for use in contact with food. **Due to the chemical structure of these FCSs, the Food and Drug Administration (FDA) considers them to belong to a class of chemicals termed "short-chain per- or polyfluorinated substances" (short-chain PFAS)** [*Emphasis added*].

That means that Daikin's FCSs, 6:2 FTOH and 5:3 acid are members of the same class of SC-PFAS because their chemical structure is similar and therefore, they are chemically-related.

FDA also treated as members of the class "the SC-PFAS monomers and the low molecular weight oligomers (LMWO) which are constituents or impurities of short-chain PFAS FCS."[42] FDA typically defines LMWOs as those below 1000 Daltons.[43] However it treats fluorinated compounds as an exception that raises the limit on Daltons to up to 2500.[44]

In other words, the SC-PFAS class consists of chemically-related substances containing alkyl chains with seven or fewer carbons where all but one of the carbons are perfluorinated. It also includes LMWOs made from or containing impurities that are SC-PFAS.

B.2. For each of the PFAS classes, the agency has determined that there is sufficient evidence that one or more members of the class biopersist, and the available toxicology data is inadequate to establish safety, and therefore the use of any member in the class cannot be considered safe.

According to 21 C.F.R. § 170.18(a), "[f]ood additives that cause similar or related pharmacological effects will be regarded as a class and in the absence of evidence to the contrary, as having additive toxic effects and will be considered as related food additives." In essence, the toxicological information for members of the class that have been studies are presumed to apply to all members of the class. FDA took this approach when it created the two classes of LC-PFAS and SC-PFAS.

B.2.1 LC-PFAS class is biopersistent and poses reproductive and developmental risks.

In defining the LC-PFAS class in 2016, the agency said it "formulated a safety assessment approach" based on:

- "structural similarities of that class to long-chain PFCAs [perfluorocarboxylic acids] and FTOHs [fluorotelomer alcohols] and
- available toxicity information on long-chain PFCAs and FTOHs that indicate a concern for reproductive/developmental toxicity."[45]

FDA relied on "published studies demonstrating metabolic conversion of FTOHs and PFCs [perfluorinated chemicals] similar in structure to the FCSs herein (perfluoroalkyl phosphate surfactants (PAPs)) to PFCAs *in vitro* and in animals."[46] It justified the approach based on the Organisation for Economic Co-operation and Development (OECD)'s Guidance for Grouping of Chemicals that essentially organized chemicals based on any one of five criteria including the:

1. Existence of common functional groups, and
2. The likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally-similar chemicals (e.g., the "metabolic pathway" approach of examining related chemicals such as acid/ester/salt).[47]

In the 2016 action removing its prior approval of three members of the LC-PFAS class,[48] the agency found these FCSs were no longer safe because "data for subsets of long-chain PFCs (demonstrating biopersistence and reproductive and developmental toxicity) are applicable to long-chain PFCs on a general basis and that this data raises significant questions as to the safety of the authorized uses of the three FCSs subject to the petition."[49]

In short, FDA determined that some members of the LC-PFAS were unsafe due to biopersistence and reproductive and developmental risks. Therefore, in the absence of evidence to the contrary, all members of the class should be considered unsafe.

B.2.2 SC-PFAS class is biopersistent and poses cancer, reproductive, developmental, immunological, and neurological risks.

In 2019, FDA made a similar determination for SC-PFAS as it had done for LC-PFAS, finding that SC-PFAS were biopersistent in the human body and that there was not enough data to demonstrate their safety.[50] Specifically, the agency sent correspondence to three companies stating that "FDA has recently become aware of toxicological data that is relevant to short-chain (SC) PFAS as a class" indicating that the new data revealed "safety concerns for SC-PFAS which are applicable" to the food contact uses authorized under FCNs 820, 827, 888, 933, 1044, 1360, and 1451 for Daikin;[51] FCN 1493 for Archroma;[52] and FCNs 599, 604, 1186 and 1676 for Asahi.[53]

The agency found that the information:

> Provides evidence that the 5:3 acid, a key metabolite of the 6:2 FTOH, is biopersistent in rodents; 6:2 FTOH may also be carcinogenic in the livers of rodents, based on data from repeated-dosing oral toxicity studies conducted with 6:2 FTOH in mice and rats; concerns for immunotoxicity and

postnatal toxicity for the 6:2 FTOH and, by extension, for the SC-PFAS monomers and the low molecular weight oligomers (LMWO) which are constituents or impurities of short-chain PFAS FCS.[54]

Due to biopersistence, FDA specifically requested more information on:

- "[Toxicokinetic] studies in rodents, hepatocytes, and kidney cells are needed to derive critical toxicokinetic parameters necessary for calculating systemic steady-state body burdens for 6:2 FTOH and its metabolites in humans and animal models."[55]
- "Longer-term repeated dose studies of at least one-year in duration are necessary to potentially derive reliable points of departure for quantitative risk assessment. Specialized studies examining functional and physiological endpoints for the immune system are recommended to fully-characterize the effects of the 6:2 FTOH on the immune system."[56]
- "[A]n extended one-generation reproductive toxicity study . . . in mice, the more sensitive species, with the 6:2 FTOH to characterize the effects of postnatal exposure on development of the immune system, nervous system, and reproductive tract."[57]
- "[C]onduct of a two-year bioassay in mice, the more sensitive species, with the 6:2 FTOH" in order "[t]o fully-characterize the carcinogenic potential of the 6:2 FTOH."[58]

In summary, FDA found that SC-PFAS as a class were biopersistent and pose cancer, reproductive and developmental risks and that the available toxicology data the companies provided to FDA was inadequate to establish safety. Therefore, as the agency concluded for LC-PFAS, all members in the class should be considered unsafe.

B.3. Despite acknowledging that LC- and SC-PFAS classes are not considered safe, FDA improperly allows food contact materials containing members of those classes to remain in use.

FDA has taken ineffective or incomplete action to stop the use of LC-PFAS and SC-PFAS despite its findings that the classes cannot be considered safe. Specifically, it:

- Allows 22 FCNs to be "voluntarily ceased" for LC-PFAS and some SC-PFAS[59] – a status that is not recognized in the law;
- Allows other FCNs to remain effective even though they contain SC-PFAS;
- Has not reviewed its existing approvals of food additives and GRAS substances to revoke uses involving LC- and SC-PFAS; and
- Has not explicitly prohibited use of LC- and SC-PFAS by issuing a regulation at 21 C.F.R. Part 189.

B.3.1 Allows 22 FCNs to be "voluntarily ceased" for LC-PFAS and some SC-PFAS – a status that is not recognized in the law.

FDA's rules at 21 C.F.R. § 170.105 provide a specific process that the agency is to follow when it determines that the intended use of a food contact substances covered by an FCN is no longer safe. According to the rules:

> (a) If data or other information available to FDA, including data not submitted by the manufacturer or supplier, demonstrate that the intended use of the food contact substance is no longer safe, FDA may determine that the authorizing FCN is no longer effective.
>
> (b) If FDA determines that an FCN is no longer effective, FDA will inform the manufacturer or supplier in writing of the basis for that determination. FDA will give the manufacturer or

supplier an opportunity to show why the FCN should continue to be effective and will specify the time that the manufacturer or supplier will have to respond.

(c) If the manufacturer or supplier fails to respond adequately to the safety concerns regarding the notified use, FDA will publish a notice of its determination that the FCN is no longer effective. FDA will publish this notice in the Federal Register, stating that a detailed summary of the basis for FDA's determination that the FCN is no longer effective has been placed on public display and that copies are available upon request. The date that the notice publishes in the Federal Register is the date on which the notification is no longer effective.

(d) FDA's determination that an FCN is no longer effective is final agency action subject to judicial review.[60]

For seven LC-PFAS in 2010 and fifteen SC-PFAS in 2019,[61] FDA took the first step of informing the manufacturers that new evidence was available to the agency regarding safety concerns for their products. The letters detailed the information the agency needed to assess whether the use of their substances continue to be safe and gave the companies an opportunity to show why the FCNs should continue to be effective.

In response to the letters, the companies provided answers that did not adequately address the safety concerns. There were three types of responses from the companies:

- Asahi offered to conduct the necessary studies but needed at least two years to perform them.[62] Citing the urgency of the risk posed by the use, Asahi stated that FDA rejected this offer.
- Chemours claimed it had permanently abandoned its three FCNs.[63]
- For LC-PFAS, BASF,[64] DuPont,[65] and Clariant [66] opted not to conduct the requested studies and offered to phase-out the use of the FCNs. For SC-PFAS, Archroma and Daikin, joined by Asahi, presented FDA with a market-based voluntary phase-out plan.[67]

Despite inadequate responses and determination of unsafe uses for all of the FCNs, FDA retained the effectiveness of all 22 FCNs and identified them as follows in its online database:

- For 10 FCNS, it says: *Introduction into interstate commerce and delivery for introduction into interstate commerce voluntarily ceased by the manufacturer*
- For 12 FCNs, FDA says: "*Introduction into interstate commerce and delivery for introduction into interstate commerce will be voluntarily ceased by the manufacturer*" (hereinafter "voluntarily ceased").[68]

This approach is inconsistent with the law and FDA's regulations and leaves the FCNs in a limbo. No one using the PFAS would be violating the law, and the manufacturers could resume the use at any time. Without delay, FDA needs to formally act to remove the effectiveness of all 22 FCNs.

B.3.2 Allows other FCNs to remain effective even though they contain SC-PFAS.

FDA designated SC-PFAS as a class of chemically-related substances with seven or fewer carbons in an alkyl chain (n-1 carbons are perfluorinated) and their LMWO which are constituents or impurities. However, the agency appears to have only focused on FCNs associated with the one member of the class – 6:2 fluorotelomer alcohol (FTOH) that it said:

> Reveals concerns for biopersistence of a key metabolite, 2H, 2H, 3H, H-perfluoroctanoic acid (5:3 acid). (CAS Reg. No. 914637-49-3). Our review of newly available toxicological data provides evidence that the 5:3 acid, a key metabolite of the 6:2 FTOH, is biopersistent in rodents; 6:2 FTOH may also be carcinogenic in the livers of rodents, based on data from repeated dosing

oral toxicity studies conducted with 6:2 FTOH in mice and rats. Our review also identifies concerns for immunotoxicity and postnatal toxicity for the 6:2 FTOH and, by extension, for the SC-PFAS monomers and the low molecular weight oligomers (LMWO) which are constituents or impurities of short-chain PFAS FCS.[69]

Unfortunately, we have seen no evidence that FDA has taken similar action on other FCNs that contain SC-PFAS. In addition, it seems to have ignored those FCNs that involve use of SC-PFAS as a processing aid in the manufacturing of plastic food packaging and food contact materials, despite the evidence that the use results in SC-PFAS migrating into food.

B.3.3 Has not reviewed its existing approvals of food additives and GRAS substances to revoke uses involving LC- and SC-PFAS.

We have seen no evidence that FDA has reviewed its food additive and GRAS approvals in its regulations at 21 CFR Part 172 to 186 for use of substances that might be members of either LC-PFAS or SC-PFAS, especially since its definition of SC-PFAS includes alkyl chains that are poly- and not necessarily perfluorinated. Given the growing evidence of a problem, such a public review is long overdue. We ask that the agency conduct that review and publicly report its findings.

B.3.4 Has not explicitly prohibited use of LC- and SC-PFAS by issuing a regulation at 21 C.F.R. Part 189.

Since both LC-PFAS and SC-PFAS were allowed for years before FDA acted, there is every reason to believe that companies self-certified their use as GRAS without notifying FDA pursuant to 21 C.F.R. Subpart E. It is particularly likely since the agency created a regulatory limbo by never publishing the notice required by 21 C.F.R. § 170.105 in the Federal Register announcing removal of effectiveness of FCNs. Since the FCNs are technically still effective, the agency would have difficulty taking enforcement action against someone using the products in food. Therefore, it is only reasonable that FDA explicitly prohibit LC-PFAS and SC-PFAS as classes by adopting a regulation in 21 C.F.R. Part 189 to protect the public from unsafe PFAS.

B.4. The agency's failure to anticipate that these two classes of PFAS were biopersistent when it authorized their use, underscores the need for FDA to reassess other PFCs, including PFAS, as their initial assessments may be similarly flawed.

There were two fundamental flaws in the FDA's assessment of SC-PFAS:

- **SC-PFAS do not biopersist.** Now we know that was just assumption based on an artificial bright line FDA drew between substances with fewer or greater than seven fully fluorinated carbons. There was not strong scientific evidence supporting that distinction as demonstrated by FDA's scientists most recent peer-reviewed publications.
- **SC-PFAS are not genotoxic and therefore there is no risk of cancer.** This is not the case. According to FDA's scientists "PFAS as a class are generally negative for activity in traditional genotoxicity tests and act primarily through non-genotoxic mechanisms of action: FDA's assessment of the endpoint of carcinogenicity for PFAS in general focused on data indicative of ability to cause peroxisome proliferation and xenobiotic-metabolism enzyme induction in the liver, which appear to be key mechanisms of action for tumor induction for PFAS compounds."[70]

We ask the agency to conduct a thorough reassessment of prior PFCs determinations and stop assuming safety based on decisions made decades ago on what is clearly an incomplete understanding of biopersistence and carcinogenicity.

PFCs to be reviewed should include those used in FDA's authorized uses in food contact applications:

- Non-stick cookware: substances may be used as a coating to make cookware non-stick.
- Gaskets, O-Rings, and other parts used in food processing equipment: substances may be used as a resin in forming certain parts used in food processing equipment that require chemical and physical durability.
- Processing aids: substances may be used as processing aids for manufacturing other food contact polymers to reduce build-up on manufacturing equipment.
- Paper/paperboard food packaging: substances may be used as grease-proofing agents in fast-food wrappers, microwave popcorn bags, take-out paperboard containers, and pet food bags to prevent oil and grease from foods from leaking through the packaging.

Other PFCs used as processing aids in the production of materials used in food contact applications should also be reviewed. Examples of these PFCs processing aids include but are not limited to propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, (HFPO-DA) also known as a substance within GenX; propanoic acid, 2,2,3,-trifluoro-3-[1,1,2,2,3,3-hexafluoro-3-(trifluoromethoxy)propoxy]-(DONA); acetic acid, 2,2-difluoro-2-[1,1,2,2-tetrafluoro-2-(1,1,2,2,2-petafluoroethoxy)ethoxy]-, (EEA-); and propanoic acid, 2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]-(HFPO-TA). [71]

Unless there is an affirmation of safety by the agency, the use of these PFCs should be presumed unsafe and FDA should take aggressive, legally required action to protect human health.

C. Environmental impact

This citizens petition is categorically excluded from the need to prepare an Environmental Assessment under 21 CFR § 25.30(h) as an "Issuance, amendment, or revocation of procedural or administrative regulations and guidance documents, including procedures for submission of applications for product development, testing and investigational use, and approval." The requested regulations and guidance documents clarify an existing statutory requirement to ensure compliance.

There is ample evidence that the chemicals persist in the environment for decades and contaminate the environment from their production, processing, use, recycling, and disposal. FDA acknowledges this when it states that "the widespread use of PFAS and their ability to remain intact in the environment means that over time PFAS levels from past and current uses can result in increasing levels of environmental contamination."[72] Therefore, stopping their use is expected to provide long-term benefits by limiting additional release of PFAS.

We have identified no extraordinary circumstances as defined at 21 CFR § 25.21 for the action requested in this petition which would require the submission of an Environmental Assessment.

D. Economic impact

Not requested by FDA.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

For more information or communications about this petition, please contact Tom Neltner at tneltner@edf.org and Maricel Maffini at drmvma@gmail.com.

Tom Neltner, Chemicals Policy Director
Environmental Defense Fund
1875 Connecticut Ave. NW
Washington, DC 20009
202-572-3263

Maricel Maffini
Independent Consultant

Frederick, MD 21701
617-470-3842

Lisette van Vliet, Senior Policy Coordinator
Breast Cancer Prevention Partners
1388 Sutter Street, Suite 400
San Francisco, CA 94109-5400
415-321-2912

Mike Belliveau, Executive Director
Defend Our Health
565 Congress Street, Suite 204
Portland, ME 04101
207-699-5795

Sue Chiang, Pollution Prevention Director
Center for Environmental Health
2201 Broadway, Suite 508
Oakland, CA 94612
510-655-3900

Melanie Benesh, Legislative Attorney
Environmental Working Group
1436 U St. NW
Washington, DC 20009
202-669-4461

Jaydee Hanson, Policy Director
Center for Food Safety
600 Pennsylvania Ave, SE
Washington DC 20003
703-231-5956

Tom Bruton, Senior Scientist
Green Science Policy Institute
P.O. Box 9127.
Berkeley, CA 94709
510-898-1739

Thomas Gremillion, Director of Food Policy
Consumer Federation of America
1620 I Street, NW
Washington, DC 20006
202-387-6121

Charlotte Brody, National Director
Jane Houlihan, Research Director
Healthy Babies Bright Futures
703 Concord Avenue
Charlottesville VA 22903

Brian Ronholm, Director of Food Policy
Consumer Reports
1101 17th St. NW - #500
Washington, DC 20036
202-744-5291

Madeleine Foote, Deputy Legislative Director
League of Conservation Voters
740 15th St. NW
Washington, DC 20009
202-454-4575

[1] US Food and Drug Administration (FDA), Per and Polyfluoroalkyl Substances (PFAS), accessed on May 22, 2021 at https://www.fda.gov/food/chemicals/and-polyfluoroalkyl-substances-pfas.
[2] Gluge J et al. 2020. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environmental Science: Processes and Impacts. Issue 12. https://doi.org/10.1039/D0EM00291G.
[3] U.S. Fire Administration, The hidden dangers in firefighting foam, accessed on May 21, 2021 at https://www.usfa.fema.gov/training/coffee_break/021120.html.
[4] FDA, Authorized uses of PFAS in food contact applications, accessed on May 22, 2021 at https://www.fda.gov/food/chemicals/authorized-uses-pfas-food-contact-applications.
[5] Balan SA et al. 2021. Regulating PFAS as a Chemical Class under the California Safer Consumer Products Program. Environ Health Perspect 129:25001. https://pubmed.ncbi.nlm.nih.gov/33595352/.
[6] Center for Disease Control and Prevention (CDC) National Biomonitoring Program, Per- and Polyfluorinated Substances (PFAS) Factsheet, accessed May 22, 2021 at https://www.cdc.gov/biomonitoring/PFAS_FactSheet.html.
[7] Environmental Working Group, Mapping the PFAS Contamination Crisis: New Data Show 2,337 Sites in 49 States, accessed on May 22, 2021 at https://www.ewg.org/interactive-maps/pfas_contamination/.
[8] The Biden Plan to Secure Environmental Justice and Equitable Economic Opportunity. https://joebiden.com/environmental-justice-plan/
[9] Grandjean P et al. 2017. Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. J Immunotoxicol. 14:188. https://pubmed.ncbi.nlm.nih.gov/28805477/.
[10] Johnson PI et al. 2014. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect 122:1028. https://pubmed.ncbi.nlm.nih.gov/24968388/.
[11] Agency for Toxic Substances and Disease Registry. 2021. Perfluoroalkyls Toxicological Profile, accessed May 22, 2021 at https://www.atsdr.cdc.gov/toxprofiledocs/index.html.
[12] EDF, The chemical industry hid evidence of harm from PFAS: 3 takeaways, May 13, 2021, accessed on May 22, 2021 at http://blogs.edf.org/health/2021/05/13/the-chemical-industry-hid-evidence-of-harm-from-pfas-3-takeaways/.
[13] Kabadi S et al. 2020. Characterizing biopersistence potential of the metabolite 5:3 fluorotelomer carboxylic acid after repeated oral exposure to the 6:2 fluorotelomer alcohol. Toxicol Appl Pharmacol 388:114878. https://pubmed.ncbi.nlm.nih.gov/31923437/.
[14] Rice PA et al. 2020. Comparative analysis of the toxicological databases for 6:2 fluorotelomer alcohol (6:2 FTOH) and perfluorohexanoic acid (PFHxA). Food Chem Toxicol 138:111210. https://pubmed.ncbi.nlm.nih.gov/32087313/.
[15] Zheng G et al. 2021. Per- and Polyfluoroalkyl Substances (PFAS) in Breast Milk: Concerning Trends for Current-Use PFAS. Environ Sci and Technol. Publication date May 13, 2021. https://pubs.acs.org/doi/10.1021/acs.est.0c06978.
[16] Toxic-Free Future, Governor Inslee Signs Ban on Nonstick Chemicals in Food Packaging, Washington is First State to Ban Fluorinated Chemicals in Packaging, March 21, 2018, accessed on May 22, 2021 at https://toxicfreefuture.org/governor-inslee-signs-ban-nonstick-chemicals-food-packaging/.
[17] Defend Our Future, First in the nation bill bans toxic chemicals from food packaging, June 7, 2019, accessed on May 22, 2021 at https://defendourhealth.org/blog/first-in-the-nation-bill-bans-toxic-chemicals-from-food-packaging/.
[18] Conservation Law Foundation, Vermont Moves to Ban Toxic Forever Chemicals in Food Containers and More, May 22, 2021, accessed on May 22, 2021 at https://www.clf.org/blog/vermont-ban-toxic-forever-chemicals-in-food-containers/.
[19] Gardella J. New York ban on PFAS in food packaging is now law. The National Law Review. December 7, 2020. https://www.natlawreview.com/article/new-york-ban-pfas-food-packaging-now-law
[20] E. I. DuPont de Nemours and Company, Letter to Mitchell A. Cheeseman, Ph.D. Acting Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, FDA, November 16, 2011. https://www.fda.gov/media/127528/download. Similar letters were sent by BASF Corporation and Clariant Corporation.
[21] FDA, Letter to E. I. DuPont de Nemours and Company Acknowledging Receipt of the Voluntary Commitment for Food Contact Substances, June 25, 2012, accessed May 22, 2021 at https://www.fda.gov/food/inventory-effective-food-contact-substance-fcs-notifications/letter-e-i-dupont-de-nemours-and-company-acknowledging-receipt-

voluntary-commitment-food-contact. Similar acknowledgment letters were sent to BASF Corporation and Clariant Corporation.

[22] Rice PA. 2015. C6-Perfluorinated compounds: The new greaseproofing agents in food packaging. Curr Envir Health Rpt 2:33. https://pubmed.ncbi.nlm.nih.gov/26231240/

[23] FDA, FDA Announces Voluntary Agreement with Manufacturers to Phase Out Certain Short-Chain PFAS Used in Food Packaging, Statement from Commissioner Stephen M. Hahn, M.D, July 31, 2020, accessed May 22, 2021, https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-agreement-manufacturers-phase-out-certain-short-chain-pfas-used-food.

[24] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, October 1, 2019. http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Daikin's response. The correspondence sent to Archroma and Asahi contains the same language. *See* http://blogs.edf.org/health/files/2021/04/Archroma-FDA-PNC-2420-PFAS_Archroma-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-14 for Archroma's response. http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Asahi's response.

[25] Rice PA et al. 2021. Comparative analysis of the physicochemical, toxicokinetic, and toxicological properties of ether-PFAS, Toxicology and Applied Pharmacology 422:15531, https://doi.org/10.1016/j.taap.2021.115531.

[26] Solvay Solexis. 4-Week Oral Toxicity Study in Rats Followed by a 2-Week Recovery Period. https://foiaonline.gov/foiaonline/api/request/downloadFile/Study%201.pdf/d87762b0-057f-4209-b967-8e665c1465ae. Study submitted to US Environmental Protection Agency under Toxic Substances Control Act Section 8(e) https://foiaonline.gov/foiaonline/api/request/downloadFile/Study%207_8e-HQ-11-18263_Redacted.pdf/403c7334-e609-4b49-ae71-69181c2606a3.

[27] 21 C.F.R. § 171.3(i); *see also* 21 U.S.C. § 348(c) 2021.

[28] FDA's definition of long-chain and short-chain PFAS may differ from Organisation for Economic Co-operation and Development's definition: Long chains refers to: perfluorocarboxylic acids (PFCAs) with carbon chain lengths C8 and higher, including perfluorooctanoic acid (PFOA); perfluoroalkane sulfonic acids (PFSAs) with carbon chain lengths C6 and higher, including perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonate (PFOS); and precursors of these substances that may be produced or present in products. See OECD, Portal for Per and Poly Fluorinated Chemicals, accessed on May 22, 2021 at https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/aboutpfass/.

[29] FDA, Letter from Dennis Keefe to George Misko of Keller and Heckman representing E. I. DuPont de Nemours & Co, June 25, 2012. See reference 2: Letter from Francis Lin (FDA) to Stephen Korzeniowski (DuPont Chemical Solutions Enterprise) dated March 4, 2008, accessed on May 22, 2021 at https://www.fda.gov/food/inventory-effective-food-contact-substance-fcs-notifications/letter-e-i-dupont-de-nemours-and-company-acknowledging-receipt-voluntary-commitment-food-contact.

[30] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, October 1, 2019. http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Daikin's response. The correspondence sent to Archroma and Asahi contains the same language. *See* http://blogs.edf.org/health/files/2021/04/Archroma-FDA-PNC-2420-PFAS_Archroma-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-14 for Archroma's response. http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Asahi's response.

[31] Warren U. Lehrenbaum of Crowell Moring on behalf of AGC Chemicals Americans, Inc., Letter to FDA's Sharon E. Koh-Fallet regarding pre-notification consultation (PNC) 2421, January 17, 2020. See pages 6 (footnote 1) to 7. http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf.

[32] FDA, FDA Announces Voluntary Agreement with Manufacturers to Phase Out Certain Short-Chain PFAS Used in Food Packaging. July 31, 2020, accessed on May 22, 2021 at https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-agreement-manufacturers-phase-out-certain-short-chain-pfas-used-food.

[33] 21 U.S.C. § 393(b).

[34] 21 C.F.R. § 171.3(i); *see also* 21 U.S.C. § 348(c).

[35] Also known as indirect food additives.

[36] FDA, Indirect Food Additives: Paper and Paperboard Components, January 4, 2016, 81 *Federal Register* 5 at 7.

[37] When FDA describes this decision on its webpage regarding the use of PFAS in food contact applications, the agency refers to the class as "long-chain PFAS," modifying its nomenclature from PFCs to PFAS. *See* FDA, Authorized Uses of PFAS in Food Contact Applications, accessed on May 22, 2021 at

https://www.fda.gov/food/chemicals/authorized-uses-pfas-food-contact-applications on horizontal tab labelled "Market Phase-Out and Revocation of Authorization of Long-Chain PFAS."
[38] FDA, Indirect Food Additives: Paper and Paperboard Components, January 4, 2016, 81 *Federal Register* 5 at 7.
[39] *Id.*
[40] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, Oct. 1, 2019, n.1, http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf.
[41] *Id.* at *1*.
[42] *Id.* at *2*.
[43] Nelson CP et al. 2011. Assessing the Toxicity of Polymeric Food Contact Substances. Food and Chemical Toxicology 49:1877. https://doi.org/10.1016/j.fct.2011.06.054.
[44] FDA, Chemistry memorandum for FCN 933 from S. Elyashiv-Barad to K. Randolph, December 1, 2009. Pages 3-4; footnote 4. http://blogs.edf.org/health/files/2021/05/Daikin-FCN-933-Chemistry-memos-CLEAN.pdf
[45] FDA, Memorandum from Dr. Penelope A. Rice to Dr. Paul Honigfort. July 27, 2015. II. Toxicology's review of information presented in FAP 4B4809; page 7, https://www.regulations.gov/document/FDA-2015-F-0714-0016.
[46] *Id.*
[47] FDA, Memorandum from Dr. Penelope A. Rice to Dr. Paul Honigfort. July 27, 2015. II. Toxicology's review of information presented in FAP 4B4809; page 7 referencing OECD, 2014, GUIDANCE ON GROUPING OF CHEMICALS, SECOND EDITION, Series on Testing & Assessment No. 194, ENV/JM/MONO(2014)4 Guidance. https://read.oecd.org/10.1787/9789264274679-en?format=pdf.
[48] FDA, Indirect Food Additives: Paper and Paperboard Components, January 4, 2016, 81 *Federal Register* 5 at 7.
[49] *Id.*
[50] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, Oct. 1, 2019, http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf.
[51] *Id.*
[52] FDA, Letter from Dr. Dennis Keefe to George G. Misko, counsel to Archroma, Oct. 1, 2019, http://blogs.edf.org/health/files/2021/04/Archroma-FDA-PNC-2420-PFAS_Archroma-Final-10-1-2019-and-response-combined.pdf.
[53] FDA, Letter from Dr. Dennis Keefe to Warren Lehrenbaum, counsel to Asahi, Oct. 1, 2019, http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf.
[54] *See supra* notes 48, 50, and 51.
[55] *Id.*
[56] *Id.*
[57] *Id.*
[58] *Id.*
[59] FDA, Inventory of Effective Food Contact Substance (FCS) Notifications, accessed May 22, 2021 at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FCN&sort=FCN_No&order=DESC&startrow=1&type=basic&search=voluntar.
[60] 21 C.F.R. § 170.105 .
[61] FDA, Inventory of Effective Food Contact Substance (FCS) Notifications, accessed at May 21, 2021 at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=fcn&sort=FCN_No&order=DESC&startrow=1&type=basic&search=interstate
[62] Warren U. Lehrenbaum of Crowell Moring on behalf of AGC Chemicals Americans, Inc., Letter to FDA's Sharon E. Koh-Fallet regarding pre-notification consultation (PNC) 2421, January 17, 2020. Pdf pages 6 (footnote 1) to 7. http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf.
[63] Chemours, Letter to FDA's Paul Honigfort for FCN No. 940, August 15, 2019, https://www.fda.gov/media/140563/download. Chemours, Letter to FDA's Paul Honigfort for FCN Nos. 885 and 1027, August 15, 2019, https://www.fda.gov/media/140564/download.
[64] BASF, Letter from Theodore Kelly Jr. Vice President, Wet End Paper Chemicals to Mitchell Cheeseman, Office of Food Additive Safety, November 28, 2011. https://www.fda.gov/media/127527/download.
[65] DuPont, Letter from John W. Moriarty, Global Business and Market Director to Mitchell Cheeseman, Office of Food Additive Safety, November 16, 2011. https://www.fda.gov/media/127528/download.

[66] Clariant, Letter from Kenneth L. Golder, President and CEO and Helmut Wagner, Global Head of Business Unit Paper to Mitchell Cheeseman, Office of Food Additive Safety, September 1, 2011. https://www.fda.gov/media/127529/download.

[67] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, October 1, 2019, http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Daikin's response. The correspondence sent to Archroma and Asahi contains the same language. *See* http://blogs.edf.org/health/files/2021/04/Archroma-FDA-PNC-2420-PFAS_Archroma-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-14 for Archroma's response. http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Asahi's response.

[68] FDA, Inventory of Effective Food Contact Substance (FCS) Notifications, accessed May 22, 2021 at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FCN&sort=FCN_No&order=DESC&startrow=1&type=basic&search=voluntar.

[69] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, October 1, 2019, http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Daikin's response. The correspondence sent to Archroma and Asahi contains the same language. *See* http://blogs.edf.org/health/files/2021/04/Archroma-FDA-PNC-2420-PFAS_Archroma-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-14 for Archroma's response. http://blogs.edf.org/health/files/2021/04/Asahi-PNC-2421-Keefe-letter-to-Asahi-counsel-10-1-19-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Asahi's response.

[70] FDA, Letter from Dr. Dennis Keefe to Devon Wm. Hill of Keller and Heckman representing Daikin, October 1, 2019, http://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf. See pages 1-5 for the FDA letter and 6-39 for Daikin's response.

[71] Rice PA et al. 2021. Comparative analysis of the physicochemical, toxicokinetic, and toxicological properties of ether-PFAS, Toxicology and Applied Pharmacology 422:15531, https://doi.org/10.1016/j.taap.2021.115531.

[72] FDA, Per and Polyfluoroalkyl Substances (PFAS), accessed on May 22, 2021 at https://www.fda.gov/food/chemicals/and-polyfluoroalkyl-substances-pfas.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
U.S. Food and Drug Administration, 5100 Paint Branch Parkway, College Park MD 20740

Memorandum

AD

Date October 1, 2002

From Division of Food Contact Substance Notification Review (DFCSNR)

Subject Worst-case estimate of the unit cancer risk for ammonium perfluorooctanoic acid (APFO)

To Regulatory Group 1-DFCSNR
Attn.: Vivian Gilliam

Through David G. Hattan, Ph.D. David G. Hattan
Toxicology Review and CAC/QRAC Coordinator

FOOD CONTACT NOTIFICATION No. 260

Dyneon LLC
6744 33rd Street North
Oakdale, Minnesota 55128
651.737.8557 (T) 651.737.9909 (F)

Submitted *via* John B. Dubeck
Keller and Heckman LLP
1001 G. Street N.W., Suite 500 West
Washington, D.C. 20001
(T) 202.434.4125 (F) 202.434.4646

RELATED PETITIONS/NOTIFICATIONS

FMF 000336 Ammonium perfluoroalkylcarboxylate (Fluorochemical FC-143)

INTRODUCTION

This memorandum calculates the worst-case unit cancer risk for ammonium perfluorooctanoic acid (APFO, CAS No 3825-26-1), (b)(4) using the most potent estimate derived from the review of two bioassays on APFO. The first assay, "Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats" was previously submitted in FMF 000336 as well as FCN 260. The "incomplete" review of this study by PML Siu, Ph.D. is located in FMF 000336 on pages 001237 - 001253 (Siu/Biddle, 03/18/1988, RE FMF 336). No conclusions were contained in the review, which was awaiting additional data prior to submission to the Cancer Assessment Committee (CAC). Interpretations of the results of this study have been aided by P. Dua, D.V.M., Ph.D (Attachment: Dua/Twaroski, 08/29/2002, RE Fluorochemical FC-143 Study in Rats - Comments).

MUTAGENICITY

APFO was negative for mutagenic activity in an Ames assay using *Salmonella typhimurium* and *Saccharomyces cerevisiae*[1], in an *in vitro* chromosome aberration assay using Chinese hamster ovary (CHO) cells[2], and in an *in vivo* micronucleus assay in mice[3]. Dyneon LLC also submitted additional mutagenicity studies on a similar compound, sodium perfluorooctanoate (SPFO, CAS No. 335-95-5). SPFO was negative for mutagenic activity in an Ames assay using *S. typhimurium* and *Escherichia coli*[4], a chromosome aberration assay using human peripheral lymphocytes[5], and in a mouse bone marrow micronucleus assay[6]. SPFO induced chromosome aberrations in CHO cells treated for short durations with ≥ 3730 µg/ml with and without metabolic activation (S9)[7].

CARCINOGENICITY

Two rat oral bioassays on APFO were submitted in FCN 260:

- "Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats", Riker Laboratories, Inc. St. Paul, Minnesota, Study No. 0281CR0012, August 1987[8]
- Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC. (2001) Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicol Sci.* 60(1):44-55.[9]

Riker Study

In the Riker study, Sprague-Dawley rats [Crl:COBSr CD(SD)BR] (50/sex/treatment) were administered FC-143 (APFO) in the diet at doses of 0, 30 and 300 ppm for 2 years. Male rats treated with 300 ppm had an increase in food consumption with a concomitant decrease in body weight, indicating that the maximum tolerated dose (MTD) was likely reached. Although females treated with 300 ppm demonstrated decreased body weights, the body weights were inconsistent and they also ate less than control animals. Mortality was slightly or significantly decreased in 300 ppm treated females or males, respectively. The study authors concluded that the compound was "not considered to be carcinogenic in the rat". The significant neoplastic findings are tabulated below.

Table 1a. Riker Study: Summary of Neoplasia Incidence - Males

Lesion	CONTROL		30 PPM		300 PPM	
	Incidence	%	Incidence	%	Incidence	%
Leydig cell adenoma	0/49	0	2/50	4	7/50	14*
Hepatocarcinoma/hyperplastic nodule[1] combined	3/49	6%	1/50	2%	8/50	16%[a]

*Statistically different from controls, p≤0 05

[1]The study authors did not address the occurrence of hepatocellular adenomas. At the time the study was conducted (1980s) hepatocellular adenoma was not a common term, but hyperplastic nodule was Hyperplastic nodules are usually classified as either foci of cellular alteration or hepatocellular adenomas Accordingly, they have been combined to address the neoplastic findings of the liver (Dua/Twaroski)

[a]Significant based on "histopatological findings in the liver, it can be stated that there is an increase in proliferative hepatocellular lesions in the high dose males compared to the control group suggesting a treatment related effect The increased incidence of non-neoplastic findings in the liver is further evidence that this is a target organ" (Dua/Twaroski).

---

[1] Griffieth, F D. and Long, J.E. (1980) Animal toxicity studies with ammonium perfluorooctanoate, *Am Ind. Hyg Assoc J* 41, 576-583 (submitted in FCN 260)

[2] Corning Hazelton Inc. study number 17388-0-437, reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260).

[3] Corning Hazelton Inc. study number 17388-0-455, reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260)

[4] Corning Hazelton Inc. study number 17073-0-409, reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260)

[5] Corning Hazelton Inc study number 17073-0-449CO, reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260)

[6] Corning Hazelton Inc. study number 17073-0-455, reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260)

[7] Corning Hazelton Inc. study number 17073-0-437CO, reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260).

[8] Reviewed by ICF for the FDA under contract number 223-00-2450, work assignment number 2002-29 (study and review included in FCN 260)

[9] Submitted in FCN 260

001978

Table 1b· Riker Study: Summary of Neoplasia Incidence - Females

Mammary Gland Lesion	CONTROL		30 PPM		300 PPM	
	Incidence	%	Incidence	%	Incidence	%
Adenocarcinoma	7/46	15	14/45	31	5/44	11
Fibroadenoma	10/46	22	19/45	42	21/44	48*
Carcinoma	1/46	2	0/45	0	0/44	0
Adenoma	3/46	6	0/45	0	0/45	0
Fibroadenomas and adenomas	13/46	28	19/45	42	21/44	48
Fibroadenomas and adenocarcinomas[1]	16/46	35	29/45	64	22/44	50

*Statistically different from controls, p≤0.05
[1]"It is appropriate to evaluate the combined incidence of benign and malignant tumors " (Dua/Twaroski)

The study authors indicated that there was a statistically significant increase ($p \leq 0.05$) in mammary gland fibroadenomas. However, analysis of the data in combination with other mammary tumor findings revealed that the combined incidence of benign and malignant tumors "does not indicate a dose relationship of mammary tumors to treatment" (Dua/Twaroski). These data, combined with the lack of lobular hyperplastic lesion findings and considering the background occurrence of mammary tumors in SD rats, lead to the conclusion that "mammary tumors in this study does not appear to be treatment related" (Dua/Twaroski). Accordingly, although the mammary fibroadenoma lesion finding was statistically significant, this data will not be used to calculate the unit cancer risk for this study.

In the absence of scientific data that suggests a more appropriate approach, the following assumptions have been made in order to calculate a unit cancer risk (UCR) for APFO based on the Riker study in rats: 1) the UCR is defined as the slope of the dose-response curve drawn from the lowest apparent effect dose of APFO to zero, 2) that tumors arising at multiple sites or from different tissues at the same site are independent of each other and are additive in calculating the UCR; 3) the lowest dose at which the incidence of neoplastic effects was significant is used to calculate the UCR, and 4) the 300 ppm·AFPO delivered in feed equates to a dose of 14.2 mg/kg/day and 16.1 mg/kg/day for males and females, respectively.

$$\text{Unit Cancer Risk}_{\text{Males}} = ((7/50–0/49)/14.2) + ((8/50\text{-}3/49)/14.2)$$
$$= 0.017 \text{ (mg/kg bw/day)}^{-1}$$

Biegel, LB, *et al*

In the Biegel, LB, *et al.* study, male Crl:CD®BR (CD) rats were feed *ab libitum*, pair fed, or fed 300 ppm C8 (APFO, rats were also fed 50 ppm Wy-14,643 as a positive control for peroxisome proliferation). Of the 156 rats/group, various numbers of animals were sacrificed at time intervals to determine hormonal measurements, cell proliferation, and for the evaluation of peroxisome proliferation. Animals were treated for 24-months, with those surviving to the end of the study (76-80/group) being euthanized and examined pathologically. The overall mean daily intake value for APFO was determined to be 13.6 mg/kg/day. The authors concluded that APFO, a peroxisome proliferator, induces a "tumor triad" increasing the incidence of tumors in the liver, Leydig cells, and pancreatic acinar cells. The tumor incidence data (Table 2 of the manuscript) and the calculated unit cancer risk derived from this data are detailed below.

Table 2: Biegel, LB, *et al*: Summary of Neoplasia Incidence

Lesion	CONTROL		PAIR FED CONTROL		APFO	
	Incidence	%	Incidence	%	Incidence	%
Liver-Adenoma/carcinoma combined	2/80	3	3/79	4	10/76	13*
Testes - Leydig cell adenoma	0/80	0	2/78	3	8/76	11*
Pancreas –acinar cell adenoma/carcinoma combined	0/80	0	1/79	1	8/76	11*

*Significantly different from the pair fed control group, $p < 0.05$.

In the absence of scientific data that suggests a more appropriate approach, the following assumptions have been made in order to calculate a unit cancer risk for APFO based on the Biegel, LB, *et al* study in rats: 1) the UCR is defined as the slope of the dose-response curve drawn from the lowest apparent effect dose of APFO to zero; 2) that tumors arising at multiple sites or from different tissues at the same site are independent of each other and are additive in calculating the UCR; 3) the lowest dose at which the incidence of neoplastic effects was significant is used to calculate the UCR; and 4) the 300 ppm AFPO delivered in feed equates to a dose of 13.6 mg/kg/day.

$$\text{Unit cancer risk} = ((10/76-3/79)/13.6) + ((8/76-2/78)/13.6) + ((8/76-1/79)/13.6)$$
$$= 0.0069 + 0.0058 + 0.0068$$
$$= 0.020 \text{ (mg/kg bw/day)}^{-1}$$

For this risk assessment, the test substance (APFO) is assumed to be a carcinogen and the sex, species and study that results in the highest unit cancer risk for the test substance is used in future risk assessments for that chemical. Two bioassays have been reviewed and both show potentially positive tumor responses in the rat to APFO and are of suitable quality to use in a quantitative risk assessment. The unit cancer risk derived from the Riker data in male rats is 0.017 $(\text{mg/kg bw/day})^{-1}$. The unit cancer risk derived from male rats in the Biegel, LB, *et al* is 0.020 $(\text{mg/kg bw/day})^{-1}$. Therefore, the worst-case unit cancer risk for APFO is 0.020 $(\text{mg/kg bw/day})^{-1}$.

CONCLUSION

This memorandum summarizes the neoplastic findings from two rat bioassays on APFO, (b)(4) being notified for in FCN 260, and the calculated unit cancer risks derived from these studies. The unit cancer risk derived from this analysis is based upon the conservative but unproven assumption that APFO is a carcinogen and that data derived from the rodent studies on APFO summarized herein can be used to estimate human cancer risk from exposure to APFO. This estimation of the unit cancer risk associated with APFO does not constitute a Center or Agency decision that the chemical is a carcinogen and data contained herein (with the exception of mutagenicity data) should be used for the sole purpose of estimating risk and not as supporting data for the development of policy or modeling of carcinogenic chemicals.

We ask your concurrence with the method used to calculate the unit cancer risk for APFO and the resulting conclusions

Michelle L. Twaroski, Ph D.
HFS-275
Attachment: Memorandum Dua/Twaroski, 08/29/2002, RE: Fluorochemical FC-143 Study in Rats – Comments

Curr Envir Health Rpt (2015) 2:33–40
DOI 10.1007/s40572-014-0039-3

FOOD, HEALTH, AND THE ENVIRONMENT (KE NACHMAN, SECTION EDITOR)

C6-Perfluorinated Compounds: The New Greaseproofing Agents in Food Packaging

Penelope A. Rice

Published online: 28 January 2015

Abstract Due to their oleophobic and hydrophobic properties and stability, perfluorinated compounds (PFCs) are used in many applications, particularly as greaseproofing agents for food contact. However, PFCs 8-carbons in length or greater (C8-PFCs) have raised concerns regarding environmental biopersistence, bioaccumulation in humans, and potent toxicity that have resulted in their gradual phase-out for food contact use. Industry has replaced C8-PFCs with shorter-chained C6-based greaseproofing agents, which are intended to have the same favorable physicochemical properties without the problematic toxicological effects in humans and wildlife. Compared with the large body of data available for C8 compounds, however, the available database on toxicity and exposure to the C6 compounds is fairly limited. This article summarizes the information in this database, focusing on aspects of human exposure and potential health risks associated with two types of C6 PFCs found in food packaging: perfluorohexanoic acid (PFHxA) and 6–2 fluorotelomer alcohol (C6-FTOH).

Keywords Perfluorinated · Fluorotelomer · PFHxA · Perfluoroalkyl · Perfluorohexanoic · Perfluorohexylethanol · C6-FTOH · Perfluorocarboxylates · Food packaging

Introduction

Perfluorinated compounds (PFCs) are composed of an alkyl chain with all of the hydrogens replaced by fluorine. This perfluorinated alkyl chain is bonded to another functional group, such as an acid, in the case of perfluorocarboxylic acids (PFCAs), or an alcohol (FTOH). Their hydrophobic and hydrophilic properties make them useful as surfactants in emulsion reactions, as reactants to make low-molecular weight perfluorinated products, and as monomers in higher molecular weight polymers. These products are used in microwave popcorn bag susceptors and greaseproofing films for paper and paperboard used in contact with oily foods, such as fast food containers and pizza boxes, as well as for other applications. While PFCAs and FTOHs are not specifically regulated by the US Food and Drug Administration (FDA), PFCAs are regulated as indirect food additives for food contact use by the FDA as surfactants and in the polymerization of high-molecular weight food contact substances (FCSs) under the 21 Code of Federal Regulations (CFR) sections 177.1380, 177.1550, 177.1615, 177.2400, and 177.2510. The use of PFCAs in the manufacture of low-molecular weight perfluorinated paper coatings was authorized in several listings for FCSs in 21 CFR 177.170 and 177.180 and Food Contact Notifications (FCNs) [1]. FTOHs are components of high-molecular weight polymeric FCSs used as coatings, which are the subject of several effective FCNs [1] for their use as greaseproofing agents in food-contact paper and paperboard.

Residual PFCAs and FTOHs derived from the manufacture of perfluorinated polymeric FCSs are present in these FCSs, and migration of these compounds into food has been demonstrated to occur as a result of the regulated uses of those FCSs [2]. As such, the FDA has historically considered the safety of PFCAs and FTOHs in the regulation of those FCSs at the dietary exposures expected to result from their migration into food. Although PFCs of eight carbons in length or greater (C8-PFCs) have a long history of regulated use since the 1960s, recent epidemiological and in vivo studies in animal models have identified concerns for persistence in serum and

This article is part of the Topical Collection on *Food, Health, and the Environment*

P. A. Rice (✉)
5100 Paint Branch Parkway, HFS-275, College Park, MD 20740, USA
e-mail: Penelope.rice@fda.hhs.gov

other bodily fluids and the environment and potent systemic and reproductive toxicity for C8-PFCs as a class [3•]. Beginning in 2006, these concerns led to regulatory actions by several agencies, including the FDA [3•] and US Environmental Protection Agency (EPA) [4, 5], resulting in voluntary agreements with industry to phase out C8-PFCs from all uses, particularly those involving direct contact with food. In the US EPA agreement, industry pledged to eliminate C8-PFCs from emissions and products by 2015. In 2013, the FDA reached a voluntary agreement with the manufacturers of five perfluorinated FCSs to eliminate production of these compounds. As a result of these agreements, industry has replaced the C8-PFC FCSs with FCSs using shorter-chained PFCs (carbon chain lengths of 6 carbons; C6-PFCs), and applications for the use of over 150 of these C6-PFC compounds have been submitted to the US EPA; these compounds are used as grease- and waterproofing paper and paperboard additives for use in contact with food and other items, anti-stain textile and carpet treatments, and tile surface treatments [6]. However, the database for the C6-based compounds is still much less extensive than that for the C8-PFCs, and these data have, as yet, not been considered as a whole in the public literature database. This article discusses the available toxicity data for C6-PFCs in the public database that are relevant for human health safety assessment, focusing on the 6–2 fluorotelomer alcohol (C6-FTOH; Fig. 1) starting material for these polymeric FCSs and perfluorohexanoic acid (PFHxA; Fig. 2), a common impurity derived from the FCS manufacturing process, and placing these data in context with data on levels in food, water, and human biological fluids. Of note, perfluorohexane sulfonate, a biopersistent C6-PFC containing a sulfonate group, is not discussed herein, as there are no C6-sulfonated PFCs authorized for use in food contact applications in the United States.

Uses and Routes of Exposure

As stated above, C6-perfluorinated telomers have similar uses to their long-chain counterparts. However, unlike the long-chain PFCs, the C6-PFCs do not appear to be used in the manufacture of non-stick cookware. It should also be noted that long-chain PFCs usually comprise a mixture of fluorotelomers varying in perfluorinated carbon length from C6 to C12 [2]; additionally, these mixed-chain-length telomers can be transformed in mammals [7] and in the

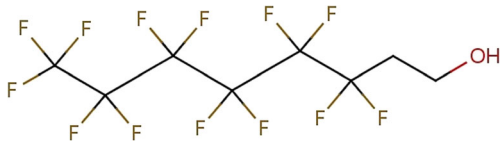


Fig. 1 PFHxA, CASRN: 307-24-4

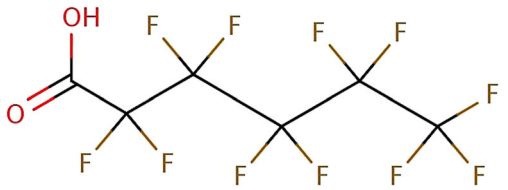


Fig. 2 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol (C6-FTOH), CASRN: 647-42-7

environment [8, 9] to PFHxA and to perfluoroheptanoate (PFHpA). As such, it should be emphasized that levels of PFHxA measured in various media, including human bodily fluids and tissues, could originate from a variety of sources, including C6- and long-chain PFCs and FTOHs, and the presence of PFHxA in these media can only rarely be directly extrapolated to direct exposure to PFHxA itself. Therefore, the recent replacement of the long-chain PFCs with C6-PFCs is unlikely to be reflected in bodily fluid PFHxA levels from human biomonitoring studies, as exposure to PFHxA from biotransformation of the C6-PFCs would simply substitute for exposure to PFHxA from biotransformation of the long-chain PFCs. Regarding C6-FTOH, studies have rarely attempted to quantify C6-FTOH content in environmental media or human tissues, except for indoor air, due to its high volatility. However, since C6-FTOH was likely present as a contaminant and biotransformation product of long-chain PFCs, C6-FTOH tissue levels are also unlikely to change significantly as a result of the replacement of long-chain PFCs with C6-PFCs.

Studies have detected PFHxA in surface waters of Victoria Harbor in Hong Kong [10•] and European riverine discharge [11] at levels of 0.15–2.24 ng/L and 2.2–32 ng/L, respectively. There are conflicting data concerning the presence of PFHxA in foods and beverages, with one critical review concluding that C6 compounds were not found at detectable levels in any type of food analyzed [12] except for low levels of PFHpA in pizza (2 ng/g), microwave popcorn (1.5 ng/g), tap water (0.64–3.02 mg/g), and bottled water (0.4 ng/g). Likewise, a recently published total diet study conducted in France [13] reported measurable levels of PFHxA at levels less than 1 ng/g in all of the food types sampled, with the highest reported levels in 'sweet and savory biscuits and bars' (0.915 ng/g), pastry and cakes (0.791 ng/g), and dairy-based desserts (0.583 ng/g); and an European Food Safety Authority (EFSA) scientific report summarizing the results of an analysis of 4,881 samples derived from various foodstuffs collected during the period 2000–2009 reported detectable levels of PFHxA in 0.9 % of samples [14]. In contrast, Zhang et al. (2011) reported levels of <0.1–0.97 ng/g PFHxA in freshwater fish and seafood [15•], and a study conducted in Catalonia, Spain reported levels of ~0.1 ng/g PFHxA in veal, fried chicken nuggets, and frankfurters [16]. There are no data on levels of possible precursors to PFHxA (FTOH, PFCs) in food and

drinking water. As may be seen from the discussion in the next section, exposure to these compounds may also contribute to PFHxA body burden.

Pharmacokinetics

PFHxA is rapidly and completely absorbed from the gut after oral administration, with no saturation of absorption noted at high doses, and is rapidly eliminated from the body via the urine without being metabolized [17••] in rats, mice, and monkeys, with only negligible percentages of the dose excreted in feces. Notably, and unlike the long-chain PFCA compounds, PFHxA is not a substrate for the renal tubule organic anion transporters (OATs) and thus is not reabsorbed from the renal filtrate, which accounts for the high efficiency of urinary elimination of PFHxA compared with longer-chain PFCAs [18]. PFHxA does not significantly accumulate in any tissue examined, except for the liver [19•], which had PFHxA levels 4- to 8-fold greater than plasma levels in mice in one study. Systemic half-lives of PFHxA in male and female rats were estimated to be 1.5–1.7 hours and 0.5–0.7 hours [17••], respectively, with elimination half-lives of 1–2 hours in both mice and rats [20••]. Elimination half-lives in cynomolgus monkeys and humans were calculated to be 1–2 days [21] and 14–49 days [20••], with no apparent gender differences. Moreover, the elimination half-lives for PFHxA were proportional to bodyweights, indicating similar volumes of distribution and elimination mechanisms between species [20••]. The C6-FTOH similarly has extremely short elimination half-lives in vivo, with 75–90 mol-% of the oral dose eliminated within 24 hours [22]. Studies conducted in rat liver microsomes observed that PFHxA and the 5:3 acid were the primary stable metabolites produced from the C6-FTOH [23••]; other stable metabolic products included the 4:3 acid, perfluorobutanoate, perfluoropentanoate, and PFHpA, all of which would be rapidly excreted in the urine. The 6–2 fluorotelomer iodide and the 6–2 fluorotelomer methacrylate were rapidly metabolized to C6-FTOH in rat liver microsomes [23••] and rat hepatocytes [24•], respectively. Perfluorinated FCSs, such as the perfluoroalkyl phosphate surfactants, can also be metabolized in vivo to their FTOH components and the corresponding FTOH metabolites [25]. Collectively, these data indicate that direct dietary exposure to perfluorinated FCSs or their perfluorinated monomeric precursors may produce toxic effects similar to exposure to the FTOH itself. As such, data from toxicity studies conducted with PFCAs and particularly with the FTOHs are directly relevant to the safety assessment of direct dietary exposure to perfluorinated polymeric FCSs.

PFHxA Biomonitoring Data

Several studies have examined serum levels of PFCs in various populations; most of the available data concern levels of C8-PFCs in biological fluids, with very few papers reporting levels of C6 compounds. There are several papers that have reported that PFHxA levels in human biological fluids (serum, milk) are below methodological limits of detection. For instance, a survey of PFC levels in umbilical cord blood samples from hospital deliveries in Ottawa, Canada reported that PFHxA levels were below the limit of detection in the majority of tested samples [26•]. Another study conducted in the general population in Hong Kong only found detectable levels of PFHxA in 40 % of the serum samples [10•], and PFHxA was not detected in any of the serum samples derived from primiparous Swedish women sampled during pregnancy and nursing [27•]. Other studies, however, have reported extremely low, but measureable, levels of PFHxA in bodily fluids from the general population ranging from 0.25 to 3 ng/ml [28•, 15•], with most samples <1 ng/ml. There is little difference in age range or limit of detection between studies that find PFHxA in sera/bodily fluids versus those that do not, and the studies were conducted over a similar time period. Thus, these differences in detection of PFHxA between studies should not be attributed to changing environmental levels. PFHxA was not detected in samples of breast milk [29•] but was detected in serum and urine taken from 5- to 13-year-old South Korean children and serum from adults of the same population [30•]. Autopsy samples of brain, lung, and liver from the general population in Catalonia, Spain reported PFHxA at mean levels of 180, 50.1, and 115 ng/g tissue, respectively [31]. The relatively high tissue levels found in the Spanish study are difficult to reconcile with the extremely low levels found in serum in most studies and with the data from pharmacokinetic studies in animals, which did not find significant accumulation of PFHxA in any tissue examined, except for low levels in liver. It is possible that the high levels of PFHxA found in this study reflect exposure to PFHxA precursors that were metabolized to PFHxA *in situ*, rather than to PFHxA itself. In fact, the extremely high levels of PFHxA found in the brain and lung in that study are consistent with possible inhalation exposure to the C6-FTOH, which has been shown to be present in ambient air at levels of up to 196 pg/m^3 [32]. Given the fact that the subjects in the Spanish study were co-exposed to PFHxA and to both C6-PFC and long-chain PFC during life, untangling the contributions of each of these exposures to the observed tissue levels would be extremely difficult and would confound any comparison with pharmacokinetic studies conducted with purified PFHxA in animals.

In conclusion, most studies report extremely low or undetectable levels of PFHxA in serum and other bodily fluids in the general population and, with a few exceptions, in foodstuffs consumed in the diet. Biomonitoring data for the C6-

FTOH and its metabolic byproducts, with the exception of PFHxA and PFHpA, are unavailable, however.

Systemic and Reproductive Toxicology

Compared with the extensive toxicological database available for the long-chain PFCs, relatively few mammalian toxicity studies have been conducted with the C6 compounds, and all of these have been conducted in rodents. For PFHxA, 90-day [33] subchronic and 2-year [34••] oral toxicity studies have been conducted in rats with the free acid, at dose ranges of 0, 10, 50, and 200 mg/kg/day for the subchronic study and doses of 0, 2.5, 15, and 100 mg/kg/day (males) and 0, 5, 30, and 200 mg/kg/day (females) in the chronic study. Ninety-day oral studies have also been conducted in rats with sodium PFHxA [35] and C6-FTOH [36••] at dose ranges of 0, 20, 100, and 500 mg/kg/day for Na PFHxA and 0, 5, 25, 125, and 250 mg/kg/day of C6-FTOH. One-generation reproductive toxicity and teratogenicity studies have been conducted with sodium PFHxA [35] and C6-FTOH [37••] in rats using the same dose ranges as the subchronic studies cited above, and a one-generation reproductive toxicity study has been conducted with PFHxA ammonium salt in mice [38••] using dose ranges of 0, 100, 350, or 500 mg/kg/day (phase I) or 0, 7, 35, or 175 mg/kg/day (phase II). A 14-day study conducted with the 6–2 methacrylate in rats is also available [24•]. The subchronic [39••], chronic [40], and developmental [41] toxicity studies conducted with PFHxA and C6-FTOH were all compliant with their respective guidelines in the FDA's Redbook. In particular, the subchronic and chronic studies gavaged rats with the test compound for 90 days and 104 weeks, respectively, and measured the following endpoints: bodyweight and feed consumption; biochemical parameters in serum and urine; hematological parameters; organ weights and histopathology; ophthalmology; and neurological function via conduct of a Functional Observational Battery (FOB).

The subchronic [33, 35, 36••] and developmental/reproductive toxicity [35, 37••, 38••] studies demonstrate that the C6 compounds share some similarities in their toxicological profiles with the C8 compounds (see below), except that PFHxA appears to be at least an order of magnitude less potent than perfluorooctanoate (PFOA). Common findings in the above-cited 90-day studies included mortality and/or decreased bodyweights, hepatocellular hypertrophy and increased liver weights, increased kidney weights, and hematological changes indicative of mild anemia at the high doses tested in these studies. However, unlike PFOA, PFHxA did not induce neoplastic effects in any organ in the chronic study [34••].

Studies noted either decreased survival or decreased bodyweights with PFHxA or C6-FTOH administration [33, 35, 36••]. Decreased survival and early mortality was noted at the highest doses tested in the chronic study [34••] with PFHxA of 100 mg/kg/day (males) and 200 mg/kg/day (females), with early mortality noted in both sexes and decreased survival noted in females only. The early mortality was associated with renal papillary necrosis and renal tubular degeneration. The C6-FTOH also induced mortality in both sexes at 250 mg/kg/day in the subchronic study, the highest dose tested, and in one female at 125 mg/kg/day [36••]. Bodyweights were not affected by treatment in either study. In contrast, significantly decreased bodyweights were noted in the subchronic studies conducted with PFHxA in males at doses of ≥50 mg/kg for the free acid and 500 mg/kg for the Na salt [33, 35], with no mortality noted.

Hepatocellular hypertrophy with increased liver weight parameters was one of the most sensitive effects noted in the subchronic studies [33, 35, 36••] and in the 14-day study [24•]; lowest observed effect levels (LOELs) from 90-day studies for this effect were 25 mg/kg/day for C6-FTOH and 100–200 mg/kg/day for PFHxA in males and 125 mg/kg/day for C6-FTOH and 500 mg/kg/day for PFHxA in females. In the chronic study [34••], hepatocellular hypertrophy was not evident at doses of up to 100 mg/kg/day (males) and 200 mg/kg/day (females); however, hepatocellular necrosis and hepatic congestion were noted in high-dose males and females. The hepatocellular necrosis observed after 104 weeks of PFHxA administration is likely the result of the enzyme induction and peroxisomal proliferation that was noted in the 90-day study. The C6-FTOH also induced single-cell hepatocellular necrosis, oval cell/biliary hyperplasia, and periportal inflammation at ≥25 mg/kg/day in males and ≥125 mg/kg/day in females after 90 days of administration [36••]. In neither study were these changes accompanied by elevations in biochemical indicators of liver injury. Interestingly, while Loveless et al. [35] noted induction of peroxisomal proliferation at the same dose levels that induced hepatocellular hypertrophy, these changes were not accompanied by alteration in serum cholesterol or triglycerides. Indeed, while all of the studies noted hepatocellular hypertrophy with C6 administration, no consistent effects on serum cholesterol profiles were reported. Supporting this finding, recent studies observed that the potency of PFHxA at the human peroxisome-proliferator activated receptor (PPAR)α, activation of which is associated with decreased blood lipid levels, is approximately half the potency of PFOA in the human hepatocellular carcinoma cell line HepG2 [42•] and approximately six-fold less potent than PFOA in both mouse and human PPARα in transiently transfected COS cells [43•]. Additionally, the decreased retention of PFHxA in the liver compared with the longer-chained compounds such as PFOA greatly decreases its potency to induce hepatic peroxisomal proliferation in vivo [44]. Concomitant with these findings, there

was also no association of PFHxA serum levels (0.03 ng/ml median) with blood lipids in a Chinese population [45•].

Subchronic studies conducted with both PFHxA and C6-FTOH noted increased kidney weight parameters [33, 35, 36••]. Kidney weight parameters were increased only in males administered PFHxA for 90 days at ≥10 mg/kg [33], whereas Na PFHxA increased kidney weight parameters in both sexes at ≥100 mg/kg/day [35]; these increases occurred in the absence of histopathological changes. However, after administration for 104 weeks, PFHxA induced renal tubular degeneration and papillary necrosis accompanied by increased urine volume and decreased specific gravity in females at 200 mg/kg/day, indicating significant adverse functional alterations in renal concentrating ability [34••]. Therefore, it would appear that the increased kidney weights in males noted in the subchronic studies represented adaptive changes to PFHxA administration, whereas the free acid of PFHxA induced renal injury in females only after chronic exposure. The reasons for this gender-specific effect of PFHxA and difference in kidney-weight response in females between the free acid and the Na salt are not apparent. For the C6-FTOH, the increased kidney weights noted in the subchronic study were accompanied by adverse histopathological changes, and the kidney appeared to be as sensitive as the liver to the adverse effects of C6-FTOH in females, with renal tubular degeneration and necrosis evident at ≥125 mg/kg/day C6-FTOH in females and at 250 mg/kg/day in males [36••].

Decreased erythrocyte parameters (erythrocyte number, hematocrit, hemoglobin) and increased reticulocyte counts were noted in both subchronic and chronic toxicity studies conducted with PFHxA at the highest doses tested, indicative of mild anemia with concomitant regenerative responses [33, 35, 36••]. While this was noted in both sexes in the subchronic study [33], anemia was only noted in females in the chronic study [34••], and the decreased erythrocyte parameters did not persist through the study duration. In contrast, the C6-FTOH induced adverse changes in the same erythrocyte parameters in the same dose range and gender pattern as was observed for hepatotoxicity [36••]. This disparity in dose ranges for this effect between PFHxA and the C6-FTOH may reflect differences in mechanism of action, the additive effect of the adverse hematopoietic effects of the various metabolites of the FTOH, and/or mechanisms secondary to the renal toxicity of the FTOH.

Ameloblast degeneration and altered tooth mineralization were noted with both the C6-FTOH [36••] and the 6–2 methacrylate [24•]; the study authors speculated that fluoride released from metabolism of the test compounds was the causative agent for the observed changes, and increased urinary fluoride levels were noted at the same doses as the adverse effects on the teeth [36••]. These effects were not seen in any of the studies conducted with PFHxA [33, 35, 34••].

No observed adverse effect levels (NOAELs) for systemic toxicity of PFHxA in the 90-day studies were 20 mg/kg/day for the sodium salt [35] and 50 and 200 mg/kg/day for the free acid in males and females, respectively [33], which are considerably higher than the 90-day no observed effect level (NOEL) of 0.06 mg/kg/day reported for the ammonium salt of PFOA in rats [46]. Similarly, the NOAEL levels for systemic toxicity in male and female rats for PFHxA in the chronic study [24•] were 15 and 30 mg/kg/day, respectively, whereas the bioassay conducted with ammonium PFOA in rats noted liver damage in treated rats down to the lowest dose tested of 1.5 mg/kg/day [47]. In contrast, both the 90-day study conducted with the C6-FTOH [36••] and an oral 90-day study conducted with the C8 fluorotelomer alcohol (8–2 FTOH) [48] reported NOAELs of 5 mg/kg/day for systemic toxicity, indicating that decreased perfluorinated chain length of the FTOH did not decrease the toxic potency under the test conditions in short-term studies.

Reproductive toxicity studies were conducted with sodium PFHxA [35] and C6-FTOH [37••] in rats and ammonium PFHxA in mice [38••]. The studies conducted with PFHxA salt and C6-FTOH gavaged male and female CD rats for ~70 days prior to mating, and pregnant females through to lactation day (LD) 22. Separate teratology studies conducted with the sodium PFHxA and C6-FTOH gavaged pregnant rats on gestation days (GD) 6–20, with terminal necropsy on GD 21. The PFHxA study in mice gavaged pregnant ICR dams from GD 6 through LD 22.

There were no effects of sodium PFHxA [35] or C6-FTOH [37••] on any reproductive indices in rats at doses of up to 500 mg/kg/day and 250 mg/kg/day, respectively; decreased maternal bodyweights and bodyweight gains were noted in the teratology [35], but not the reproductive, cohort at 500 mg/kg/day PFHxA and in both cohorts at 250 mg/kg/day C6-FTOH [37••]. There were no effects of sodium PFHxA on reproductive organ weights or histopathology in the P0 generation. The only developmental effects of sodium PFHxA noted were a 17–18 % decrease in mean pup weight throughout the lactation period in the F1 generation in the one-generation study and 10 % decreased fetal weight in the teratology study at 500 mg/kg/day, the highest dose tested in both studies. For the C6-FTOH [37••], the reproductive study noted increased pup mortality and decreased pup weights at ≥125 mg/kg/day; increased incidences of delayed ossification and wavy ribs were noted in the teratology study at these doses. The NOELs for prenatal and postnatal toxicity in rats from these studies were 300 mg/kg/day PFHxA and 25 mg/kg/day C6-FTOH. In contrast, mice were far more sensitive to the effects of PFHxA. Decreased bodyweight gains during postnatal days (PNDs) 0–4 (≥350 mg/kg/d) and the entire lactation period (500 mg/kg/d) were noted in dams [38••]. Significant litter observations (mostly at≥350 mg/kg/d) included increased incidences of stillbirths, increased whole

litter loss on PNDs 0–3, decreased pup survival during lactation, decreased pup bodyweights, delayed eye opening, and reduced terminal bodyweights in F1 females and terminal bodyweight : liver weight ratios in F1 males. At 175 mg/kg/day, significant findings included increased numbers of stillborn pups and pups dying on PND 1 and decreased pup weight at PND 1. The NOEL for developmental toxicity of PFHxA salt in mice from the study is 35 mg/kg/day. The adverse effects noted on pup bodyweight, postnatal survival, and attainment of developmental landmarks are consistent with effects noted in mice after PFOA administration; however, the LOELs for these effects in the study conducted with PFHxA are at least two orders of magnitude greater than the respective LOELs for PFOA in mice, the most sensitive species [49], of 0.6 mg/kg/day and 1 mg/kg/day, respectively, emphasizing the decreased potency of the C6 compound compared with PFOA.

In summary, subchronic and chronic oral toxicity studies conducted with PFHxA (free acid and sodium salt) reported an array of toxicological effects that are broadly similar to those noted with PFOA: decreased bodyweights, hepatocellular hypertrophy and peroxisomal proliferation, and anemia. Kidney effects were more pronounced with PFHxA versus PFOA; but the data overall demonstrate that PFHxA is much less toxic than PFOA, with LOELs at least an order of magnitude higher for PFHxA than PFOA. Moreover, PFHxA was non-carcinogenic in rats and did not display the potent postnatal toxicity noted with PFOA in either rats or mice.

In contrast, the toxicological profile for the C6-FTOH is not as well characterized. Subchronic studies conducted with the C6-FTOH identify similar toxic endpoints to those identified for the 8–2 FTOH, with adverse effects on the teeth, the kidneys, the liver, and red blood cell homeostasis. However, the mortality noted during the C6-FTOH study was not seen with the 8–2 FTOH, and the adverse effects on the kidney were more severe in the C6-FTOH study. As such, while the toxicological profile for PFHxA itself appears less concerning than that for long-chain PFCAs, the toxicological profile and potency for the C6-FTOH may be similar to the long-chained FTOHs. Future studies are needed to confirm whether this is the case.

Conclusions

PFCAs and FTOHs have been used in a variety of applications, including food packaging. Human exposure to these compounds has been demonstrated, with diet as a significant contributor, although the significance of exposure from food packaging has not been elucidated. Due to concerns regarding the toxicological profile of C8-PFCs, industry has phased out use of this class of compounds, replacing them with C6-based PFCs. Although the existing toxicological database for the C6-PFCs is, as yet, comparatively sparse, these compounds do not appear to possess the biopersistence and potent systemic and reproductive toxicity that are characteristic of C8-PFCs as a class. Instead, data from animal and epidemiological studies indicate that C6-PFCs are rapidly and completely excreted and do not appear to accumulate in biological fluids. Of the two C6 compounds discussed in this article, PFHxA has been well characterized in rodent models. PFHxA has a similar profile of toxicological effects to PFOA based on in vivo subchronic studies in rodents; however, the lack of bioaccumulation in the liver significantly decreases the potency of PFHxA, leading to NOAEL values that are at least an order of magnitude higher than the respective NOAEL values for long-chain PFCs. Moreover, PFHxA has been demonstrated to be non-carcinogenic in rodents, unlike PFOA, and appears to be a far less potent postnatal toxicant. In contrast, significant data gaps remain in the toxicological profile of C6-FTOH. The pharmacological profile of this compound in humans and rodents in vivo is not well characterized, and data from biomonitoring studies determining levels of this compound or its metabolites in human biological fluids are lacking. Data on the chronic, reproductive, and developmental toxicity of this compound are also scanty, as there are no available studies examining the toxicological profile of the C6-FTOH in mice, which have been shown to be more sensitive to the toxicological effects of PFCs than rats. Given the fact that toxicity data for the FTOHs are highly pertinent to the safety evaluation of dietary exposure to perfluorinated PFCs, confirmation that the C6-PFC compounds are a safer alternative to the long-chain PFCs awaits data from appropriately designed studies conducted with the C6-FTOH that address these data gaps.

Compliance with Ethics Guidelines

Conflict of Interest Penelope A. Rice declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest and published recently are highlighted below as:
- • Of importance
- •• Of major importance

1. US FDA (2013) Inventory of effective food contact substance (FCS) notifications. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/Notifications/ucm116567.htm. Accessed 2 Aug 2014.

2. Begley TH, White K, Honigfort P, et al. Perfluorochemicals: potential sources of and migration from food packaging. Food Addit Contam. 2005;22(10):1023–31.
3.• US FDA (2012), Update on perfluorinated grease-proofing agents. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/Notifications/ucm308462.htm. Accessed 2 Aug 2014. *Voluntary agreement between US FDA and industry phasing out use of 3 long-chain perfluorinatedFCSs.*
4. US EPA (2009) Long-chain perfluorinated chemicals action plan. http://www.epa.gov/oppt/existingchemicals/pubs/pfcs_action_plan1230_09.pdf. Accessed 2 Aug 2014.
5. US EPA (2013) 2010/2015 PFOA Stewardship Program. http://www.epa.gov/oppt/pfoa/pubs/stewardship/index.html. Accessed 2 Aug 2014.
6. US EPA (2014) Perfluorooctanoic acid and fluorinated telomers: New chemical review of alternatives for PFOA and related chemicals. http://www.epa.gov/oppt/pfoa/pubs/altnewchems.html#3. Accessed 18 Nov 2014.
7. Fasano WJ, Sweeney LM, Mawn MP, et al. Kinetics of 8–2 fluorotelomer alcohol and its metabolites, and liver glutathione status following daily oral dosing for 45 days in male and female rats. Chem Biol Interact. 2009;180(2):281–95.
8. Wang N, Szostek B, Buck RC, et al. 8–2 Fluorotelomer alcohol aerobic soil biodegradation: Pathways, metabolites, and metabolite yields. Chemosphere. 2009;75:1089–96.
9. Lee H, D'eon J, Mabury SA. Biodegradation of perfluoroalkyl phosphates as a source of perfluorinated acids to the environment. Environ Sci Technol. 2010;44(9):3305–10.
10.• Loi EIH, Yeung LWY, Mabury SA, et al. Detections of commercial fluorosurfactants in Hong Kong marine environment and human blood: A pilot study. Environ Sci. 2013;47:4677–85. *Only 40 % of human blood samples had detectable PFHxA; one of predominant perfluorinated compounds in water samples from Victoria Harbor.*
11. McLachlan MS, Holmstrm KE, Reth M, et al. Riverine discharge of perfluorinated carboxylates from the European continent. Environ Sci Technol. 2007;41:7260–5.
12. Pico Y, Farre M, Llorca M, et al. Perfluorinated compounds in food: A global perspective. Crit Revs Food Sci Nutr 2011; 1, doi: 10.1080/10408391003721727.
13. Riviere G, Sirot V, Tard A, et al. Food risk assessment for perfluoroalkyl acids and brominated flame retardants in the French population: Results from the second French total diet study. Sci Total Environ. 2014;491–492:176–83.
14. European Food Safety Authority Results of the monitoring of perfluoroalkylated substances in food in the period 2000–2009. EFSA J 2011; 9(2):2016.
15.• Zhang T, Sun H, Lin Y, et al. Perfluorinated compounds in human blood, water, edible freshwater fish, and seafood in China: Daily intake and regional differences in human exposures. J Agric Food Chem. 2011;59(20):11168–76. *Mean (detection frequency) human blood and freshwater fish and seafood PFHxA levels in four locations in China: 0.27 ng/ml blood (39 % of samples) and 0.07 ng/g wet weight (3 % of samples).*
16. Jogsten IE, Perilio G, Llebaria X, et al. Exposure to perfluorinated compounds in Catalonia, Spain, through consumption of various raw and cooked foodstuffs, including packaged food. Food Chem Toxicol. 2009;47:1577–83.
17.•• Gannon SA, Johnson T, Nabb DL, et al. Absorption, distribution, metabolism, and excretion of [1-14C]-perfluorohexanoate ([14C]-PFHx) in rats and mice. Toxicology. 2011;243:55–62. *Maximum plasma concentration after oral dosing: 30 min (male rats), 15 min (female rats), 15–30 min (mice). No metabolism in rat or mouse hepatocytes; 100 % urinary excretion within 24 h.*
18. Yang C-H, Glover KP, Han X. Characterization of cellular uptake of perfluorooctanoate via organic anion-transporting polypeptide 1A2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates. Toxicol Sci. 2010;117(2):294–302.
19.• Iwai H. Toxicokinetics of ammonium perfluorohexanoate. Drug Chem Toxicol. 2011;34(4):341–6. *Recovery 90 % of oral dose within 24 h in mice and rats; major route of elimination in urine (≥85 %). Tissue levels of PFHxA below LOD 168 h after dosing, except for liver. No difference in toxicokinetics between single and repeated dosing.*
20.•• Russell MH, Nilsson H, Buck RC. Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat, and monkey. Chemosphere. 2013;93(10):2419–25. *Apparent elimination half-life 14–49 d in humans, based on ski-wax workers exposed via inhalation to 6–2 FTOH.*
21. Chengelis CP, Kirkpatrick JB, Myers NR, et al. Comparison of the toxicokinetic behavior of perfluorohexanoic acid (PFHxA) and nonafluorobutane-1-sulfonic acid (PFBS) in cynomolgus monkeys and rats. Reprod Toxicol. 2009;27(3–4):400–6.
22. Gannon SA, Mawn MP, Munley SW, et al. Toxicokinetic evaluation of 6:2 fluorotelomer alcohol and metabolites in rats following 90 days or oral exposure. Toxicol-Off J Soc Toxicol. 2012;126(1):402.
23.•• Ruan T, Sulecki LM, Wolstenholme BW, et al. 6:2 fluorotelomer iodide in vitro metabolism by rat liver microsomes: Comparison with [1,2-14C] 6:2 fluorotelomer alcohol. Chemosphere. 2014;112:34–41. *Six stable biotransformation products: 5:3 acid, 4:3 acid, PFBA, PFPeA, PFHxA, PFHpA; Five transient products: 6:2 FTCA, 6:2 FTUCA, 5:2 ketone, 5:2 sFTOH, and 5:3 Uacid. Similar metabolic profile for 6:2 FTI.*
24.• Anand SS, Serex TL, Carpenter C, et al. Toxicological assessment of tridecafluorohexylethyl methacrylate (6:2 FTMAC). Toxicology. 2012;292:42–52. *6:2 FTMAC non-mutagenic in Ames test and mouse lymphoma assay; induced structural aberrations in absence of S9 in human lymphocytes, but did not induce numerical aberrations and was non-clastogenic in vivo. Test substance-related effects in 14-day oral toxicity test in Sprague–Dawley rats: increased liver, kidney, and thyroid weights with minimal hepatocyte hypertrophy and altered mineralization of teeth and femur.*
25. D'eon JC, Mabury SA. Production of perfluorinated carboxylic acids (PFCAs) from the biotransformation of perfluoroalkyl phosphate surfactants (PAPS): Exploring routes of human contamination. Environ Sci Technol. 2007;41:4799–805.
26.• Arbuckle TE, Kubwabo C, Walker M, et al. Umbilical cord levels of perfluoroalkyl acids and polybrominated flame retardants. Int J Hyg Environ Health. 2013;216:184–94. *PFHxA levels less than limit of detection in the majority of umbilical cord blood samples from hospital deliveries in Ottowa, Canada.*
27.• Glynn A, Berger U, Bignert A, et al. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: Serial sampling during pregnancy and nursing, and temporal trends 1996–2010. Environ Sci Technol. 2012;46:9071–9. *PFHxA not detected in any sample.*
28.• Guo F, Zhong Y, Wang Y, et al. Perfluorinated compounds in human blood around Bohai Sea, China. Chemosphere. 2011;85:156–62. *Mean and median whole blood PFHxA levels in Chinese cities in Bohai Sea area: 0.51 and 0.4 ng/ml, detection frequency: 99 %. No gender difference or age difference in levels.*
29.• Kubwabo C, Kosarec I, Lalonde K. Determination of selected perfluorinated compounds and perfluoroalkyl phosphate surfactants in human milk. Chemosphere. 2013;91:771–7. *PFHxA not detected.*
30.• Kim D-H, Lee M-Y, Oh J-E. Perfluorinated compounds in serum and urine samples from children aged 5–13 years in South Korea. Environ Pollut. 2014;192:171–8. *Mean (detection frequency) PFHxA in urine (adults and children) and serum (children): 1.38 (5 %), 0.731 (11 %), and 0.353 (8 %) ng/ml, respectively, in South Korean survey.*

31. Perez F, Nadal M, Navarro-Ortega A, et al. Accumulation of perfluoroalkyl substances in human tissues. Environ Intl. 2013;59:354–62. *Postmortem tissue levels of PFHxA in 20 subjects from Tarragona County in Spain: 68.3 ng/g liver, main compound in brain (10.1–486 ng/g), 207 ng/g lung.*
32. Fromme H, Tittlemier SA, Volkel W, et al. Review: Perfluorinated compounds—Exposure assessment for the general population in western countries. Int J Environ Health. 2009;212(3):239–70.
33. Chengelis CP, Kirkpatrick JB, Radovsky A, et al. A 90-day repeated dose oral (gavage) toxicity study of perfluorohexanoic acid (PFHxA) in rats (with functional observational battery and motor activity determinations). Reprod Toxicol. 2009;27:342–51.
34.•• Klaunig JE, Shinohara M, Iwai H, et al. Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHA) in Sprague–Dawley rats. Toxicol Pathol. 2014;20:1–12. *PFHA did not induce tumors at any dose; treatment related effects: decreased survival (females), early mortality (both sexes), hepatocellular necrosis and congestion (both sexes), erosion/ulceration of glandular and nonglandular stomach (females), renal tubular necrosis and papillary degeneration (females), pulmonary congestion/hemorrhage and increased alveolar macrophages (both sexes).*
35. Loveless SE, Slezak B, Serex T, et al. Toxicological evaluation of sodium perfluorohexanoate. Toxicology. 2009;264:32–44.
36.•• Serex T, Anand S, Munley S, et al. Toxicological evaluation of 6:2 fluorotelomer alcohol. Toxicology. 2014;319:1–9. *Subchronic NOAEL 5 mg/kg/d based on hematological and liver effects; mortality and renal toxicity observed at higher doses. Nonmutagenic in Ames and mouse lymphoma; nonclastogenic in human lymphocyte chromosome aberration assay.*
37.•• O'Connor JC, Munley SM, Serex TL, et al. Evaluation of the reproductive and developmental toxicity of 6:2 fluorotelomer alcohol in rats. Toxicology. 2014; 317: 6–16. *Reproductive NOEL >250 mg/kg (highest dose tested). Parental NOELs 25 mg/kg/d, for decreased feed consumption and bodyweight parameters at ≥125 mg/kg/d. Developmental NOEL of 25 mg/kg/d for increased delayed ossification and wavy ribs (teratology study) and pup mortality and decreased bodyweights (reproductive study) at ≥125 mg/kg/d.*
38.•• Iwai H, Hoberman AM. Oral (gavage) combined developmental and perinatal/postnatal reproduction toxicity study of ammonium salt of perfluorinated hexanoic acid in mice. Int J Toxicol. 2014;33:219–37. *Maternal and reproductive NOAEL = 100 mg/kg/d in ICR mice. Maternal effects at ≥350 mg/kg/d: mortality, excess salivation, decreased bodyweight gains. Developmental effects: stillbirths, decreased viability indices, delayed physical development.*
39. US FDA Toxicological Principles for the Safety Assessment of Food Ingredients–*Redbook 2000.* Chapter IV.C.4.a. Subchronic Toxicity Studies with Rodents, 11/03. Accessed at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm078345.htm on 12/4/14.
40. US FDA Toxicological Principles for the Safety Assessment of Food Ingredients–*Redbook 2000.* Chapter IV.C.7. Combined Chronic Toxicity/Carcinogenicity Studies with Rodents, 11/03. Accessed at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm078393.htm on 12/5/14.
41. US FDA Toxicological Principles for the Safety Assessment of Food Ingredients–*Redbook 2000.* Chapter IV.C.9.b. Guidelines for Developmental Toxicity Studies, 7/00. Accessed at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm078399.htm on 12/4/14.
42.• Buhrke T, Kibellus A, Lampen A. In vitro toxicological characterization of perfluorinated carboxylic acids with different chain lengths. Toxicol Lett. 2013;218:97–104. *Concentration of 20 % effect (C20 %) values for PFHxA ~10-fold, ~20-fold, and 2-fold respective values for PFOA in cytotoxicity, proliferation, and PPARα-activation assays in HepG2 cells; negative in V79 micronucleus and Ames assays.*
43.• Wolf CJ, Schmid JE, Lau C, et al. Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARα) by perfluoroalkyl acids (PFAAs): further investigation of C4-C12 compounds. Reprod Toxicol. 2012;33:546–51. *10-fold higher no observed effect concentration for PFHxA versus PFOA activation of human and mouse PPARα in transfected COS cells.*
44. Kudo N, Suzuki-Kakajima E, Mitsumoto A, et al. Responses of the liver to perfluorinated fatty acids with different carbon chain length in male and female mice: In relation to induction of hepatomegaly, peroxisomal β-oxidation, and microsomal 1-acylglycerophosphocholine acyltransferase. Bio Pharm Bull. 2006;29(9):1952–7.
45.• Fu Y, Wang T, Fu Q, et al. Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population. Ecotoxicol Environ Saf. 2014;106:246–52. *PFHxA detected in ~77 % samples, 0.03 ng/ml (median).*
46. Perkins RG, Butenhoff JL, Kennedy GL, et al. 13-Week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drug Chem Toxicol. 2004;27(4):361–78.
47. Butenhoff JL, Kennedy GL, Chang S-C, et al. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague–Dawley rats. Toxicology. 2012;298:1–13.
48. Ladics GS, Kennedy GL, O'Connor J, et al. 90-Day oral gavage toxicity study of 8–2 fluorotelomer alcohol in rats. Drug Chem Toxicol. 2008;31(2):189–216.
49. Abbott BD, Wolf CJ, Schmid JE, et al. Perfluorooctanoic acid – induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator-activated receptor alpha. Toxicol Sci. 2007;98(2):571–81.

NATURAL RESOURCES DEFENSE COUNCIL
BREAST CANCER FUND
CENTER FOR ENVIRONMENTAL HEALTH
CENTER FOR FOOD SAFETY
CENTER FOR SCIENCE IN THE PUBLIC INTEREST
CHILDREN'S ENVIRONMENTAL HEALTH NETWORK
CLEAN WATER ACTION
ENVIRONMENTAL WORKING GROUP
IMPROVING KIDS' ENVIRONMENT

October 17, 2014 (REVISED FROM VERSION FILED October 16, 2014)

Dr. Dennis Keefe
Director of the Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740

Re: Petition seeking amended food additive regulation to remove FDA's approval at 21 C.F.R. § 176.170 of the use of long-chain perfluorocarboxylate oil and grease repellents in paper and paperboard - Pre-Notification Consultation 1417 (PNC 1417)

Dear Dr. Keefe:

In 2010, the U.S. Food and Drug Administration's (FDA) food additives toxicologists concluded that, in animal studies, long-chain perfluorinated compounds adversely affect fetal and newborn development and that one group of these compounds, long-chain perfluorocarboxylates[1], adversely affect the male, and, possibly the female, reproductive systems.[2] A 'long-chain' means the compound has eight or more carbons ("≥ C8") connected together and the carbons are saturated with fluorine atoms. As the chain lengthens, FDA's toxicologists noted that the chemical's biopersistence, and hence potency, in the human body increases.[3] These findings on long-chain perfluorocarboxylates expand on the toxicologist's 2007 conclusion that carcinogenicity was a concern for chemicals that were structurally similar to the perfluorooctanoic acid (PFOA).[4]

The agency's food additive toxicologists stated that "[d]ue to the considerable uncertainties remaining regarding the toxic effects of perfluorinated compounds as a class in humans, significant questions remain regarding the safe levels of dietary exposure to ≥ C8 perfluorinated

[1] Including chemicals that may be converted to perfluorocarboxylates.
[2] FDA Memo from Toxicology Group I to Regulatory Group 2 on September 30, 2010 at page 34-35.
[3] *Ibid*., p. 34-35.
[4] *Ibid*., p. 1.

compound such that additional testing is recommended to ensure safety."[5] In other words, without additional testing, there was no longer a reasonable certainty of no harm from the intended uses of the long-chain perfluorinated compounds.

Based on this conclusion, FDA took the unprecedented step of asking three companies with effective Food Contact Substance notifications (FCN) for perfluorocarboxylates to cease their sale and distribution in the United States.[6] In 2011, all three voluntarily agreed.[7]

Despite this important step, three classes of long-chain chemicals that are likely to be converted to perfluorocarboxylates[8] continue to be allowed to be used in paper and paperboard under FDA's indirect food additive regulations at 21 C.F.R. § 176.170(a)(5). Table 1 and Appendix 2 provide details for each class.

Table 1: Three classes of long-chain perfluorocarboxylates that NRDC is requesting FDA to remove from 21 C.F.R. § 176.170

Class	Description of indirect additive[a]	Company Requesting Approval	Year Approved	Max. Estimated Exposure[b]
1	Diethanolamine salts of mono- and bis (1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C8-C18 and the salts have a fluorine content of 52.4% to 54.4% as determined on a solids basis	DuPont	1967	0.013 mg / person / day
2	Pentanoic acid, 4,4-bis [(*gamma-omega*-perfluoro-C8-20-alkyl)thio] derivatives, compounds with diethanolamine (CAS Reg. No. 71608-61-2)	Ciba-Geigy[c] (now BASF)	1983	0.05 mg / person / day
3	Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma], [omega]-perfluoro C4-20 alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide	Ciba-Geigy[c] (now BASF)	1996 & 1997	0.13 mg / person / day

[a] See Appendix 2 for details on each class.
[b] See Appendix 3.
[c] Ciba-Geigy transferred this business to Ciba Specialty Chemicals in 1996. BASF purchased it in 2008.

Because the agency did not follow-up its initiative on the above mentioned FCNs by taking the critical next step of revoking these approvals made decades earlier, any company, even those not

[5] *Ibid*., p. 36.
[6] See Appendix 6 for a description of the seven FCNs.
[7] *Ibid*.
[8] For convenience, we refer to chemicals that are likely to be converted to perfluorocarboxylates as part of the class of perfluorocarboxylates.

requesting FDA's approval, can continue using the chemicals listed on Table 1in pizza boxes, sandwich wrappers, and other food packaging without FDA's or the public's knowledge. While the shutdown of domestic production of these chemicals has minimized their use and most food product manufacturers may no longer rely on them, new overseas production in China and India could easily fill the void without FDA's knowledge.

After reviewing the literature[9] published since FDA reached its conclusions that there was insufficient scientific data supporting the safety of long-chain perfluorocarboxylates, the Natural Resources Defense Council (NRDC) found that the evidence of adverse health effects caused by these chemicals has only strengthened since 2010. We identified 10 additional animal studies, an epidemiological study and three systematic reviews that were published between 2009 and 2014. All supported FDA's toxicology conclusions that significant gaps remain in our knowledge of the safety of long-chain perfluorocarboxylates regarding pre-natal and post-natal developmental toxicity endpoints, reproductive health and function in males, and reproductive health in females. Particularly compelling were
1) A systematic, objective and transparent review of the scientific literature on PFOA concluding that there is sufficient human evidence that developmental exposure to PFOA reduces fetal growth;[10] and
2) The U.S. Environmental Protection Agency's (EPA) draft comprehensive analysis[11] of the health effects of PFOA released in February 2014. EPA's draft report established a reference dose[12] of 0.00002 mg PFOA per kg of body weight per day (mg/kg-bw/day). For comparison, a 60 kg adult consuming 3 kg of food a day and the maximum exposure estimates listed in Table 1 would have an Estimated Daily Intake (EDI) for the three classes of additives would range from 0.00022 to 0.0022 mg/kg-bw/day – 10 to 100 times greater than EPA's draft Reference Dose for PFOA.

We understand that PFOA may be only a small component in the three classes of perfluorocarboxylates in Table 1 and the chemicals may not be readily metabolized to PFOA in the body. However, they are structurally similar, leading us to conclude that the FDA's concerns about the health effects of PFOA in 2010 also apply to the three classes of chemicals mentioned above. Therefore, perfluorocarboxylates are:

- Likely to adversely affect fetal and neonatal development;
- Likely to adversely affect the male, and, possibly the female, reproductive systems; and
- Likely to cause cancer.

[9] See Appendix 4 and 5 for review.
[10] Johnson PI et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1028-1039. http://dx.doi.org/10.1289/ehp.1307893
[11] EPA, External Peer Review of EPA's Draft Health Effects Documents for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS), http://peerreview.versar.com/epa/pfoa/. (Accessed March 17, 2014). The two documents are "Health Effects Document for Perfluorooctanoic Acid (PFOA)" (EPA Doc. No. 822R14001) and "Health Effects Document for Perfluorooctane Sulfonate (PFOS)" (EPA Doc No. 822R14002) (2014).
[12] For dietary exposures, a reference dose is developed in a manner consistent with FDA's Acceptable Daily Intake or ADI.

These effects are even more significant because these chemicals, like PFOA, are likely to persist in the human body in ways not fully understood decades ago when FDA made its original safety decisions to approve the use of these chemicals.

Given the dearth of toxicology studies on these three classes of chemicals, without evidence showing that these chemicals impact the human body differently than PFOA, there is no longer "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" as required by the FFDCA and 21 C.F.R. Parts 170 and 171. In other words, the uses allowed by the rule are not safe per 21 C.F.R. § 170.3(i).

Therefore, the Natural Resources Defense Council (NRDC) submits this food additive petition, pursuant to section 409(b)(l) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 C.F.R. § 171.130, requesting that FDA revoke the approved uses of the perfluorocarboxylates in 21 C.F.R. § 176.170 as described in Table 1.[13]

By making this change, any company seeking to use long-chain perfluorocarboxylates would need to notify FDA by submitting a FCN or food additive petition before commencing the use.

Acceptance of this petition would complement actions taken by the U.S. Environmental Protection Agency (EPA) pursuant to the Toxic Substance Control Act (TSCA).[14] Using Section 5 of TSCA, EPA has issued Significant New Use Restrictions (SNURs) under 40 C.F.R. §§ 721.982 and 721.10536 from 2000 to 2013 that today require the agency be notified of new uses of various long-chain perfluorinated compounds.[15] If a chemical's use is subject to a SNUR, the importer or manufacturer must notify the EPA 90 days before commencing import or manufacture.

In addition, in 2006 EPA prohibited the use of Class 2 perfluorcarboxylate in Table 1 as an inert ingredient in pesticides applied to food because the potential risks meant the agency was unable to determine that the use met the safety requirements of the Section 408(c)(2) of the Federal Food Drug and Cosmetic Act.[16] The reasonable certainty of no harm safety standard used by EPA to make it decision is essentially the same as the one FDA must use for food additives.

Therefore, we request that FDA revoke the approvals it granted decades ago for the three classes of long-chain perfluorocarboxylates listed in Table 1 from 21 C.F.R. § 176.170. See Appendix 1 for additional details on the petition and Appendix 7 for the specific changes we seek in the regulation. This letter and all appendices constitute our complete petition. Please note that this is NOT a citizens petition. We have enclosed three copies per 21 C.F.R. § 171.1.

If you have questions or comments, please contact Erik D. Olson at eolson@nrdc.org.

[13] See Appendix 1 for the information requested by FDA at 21 C.F.R. § 171.130.
[14] Because TSCA exempts chemicals used to make food, drugs, medical devices, and cosmetics regulated by FDA at 15 U.S.C. § 2602(2)(B)(vi), EPA's SNURs do not apply to long-chain perfluorinated compounds used in as food additives including food contact substances.
[15] 78 Fed. Reg. 62,451 (Oct. 22, 2013).
[16] 72 Fed. Reg. 45,409 (August 9, 2006).

Sincerely,

Erik D. Olson, Senior Strategic Director for Health and Food
Maricel Maffini, Ph.D., Consulting Senior Scientist
Natural Resources Defense Council
1152 15th St. NW, Suite 300
Washington, DC 20005
Phone 202-289-6868

Caroline Cox, Research Director
Center for Environmental Health
2201 Broadway, Suite 302
Oakland, CA 94612
Caroline@ceh.org (Caroline Cox)

Delores E. Weis, Executive Director
Tom Neltner
Improving Kids' Environment (IKE)
1915 W. 18th Street
Indianapolis, Indiana 46202
dweis@ikecoalition.org

Donna F. Solen, Senior Attorney
Center for Food Safety
303 Sacramento Street
Second Floor
San Francisco, CA 94111
Email: dsolen@centerforfoodsafety.org

Lynn Thorp, National Campaigns Director
Clean Water Action
1444 Eye Street NW, Suite 400
Washington, DC 20005-6538
lthorp@cleanwater.org

Michael F. Jacobson, PhD, Executive Director
Lisa Y. Lefferts, MSPH, Senior Scientist
Center for Science in the Public Interest
1220 L Street, NW, Suite 300
Washington, DC 20005
LLefferts@cspinet.org

Nsedu Obot Witherspoon, MPH, Executive Director
Children's Environmental Health Network
110 Maryland Avenue, NE, Suite 402
Washington, DC 20002
nobot@cehn.org

Scott Faber, Vice President for Government Relations
Environmental Working Group
1436 U St. NW
Suite 100
Washington, DC 20009
sfaber@ewg.org

Nancy Buermeyer, Senior Policy Strategist
Breast Cancer Fund
1388 Sutter Street, Suite 400
San Francisco, CA 94109
nbuermeyer@breastcancerfund.org

List of Appendices:

- Appendix 1: Responses to Elements Required by 21 C.F.R. § 171.1
- Appendix 2: Description of each of the three classes of long-chain perfluorocarboxylates
- Appendix 3: FDA's related estimated daily intakes for perfluorocarboxylates
- Appendix 4: Toxicology assessment for three classes of long-chain perfluorocarboxylates
- Appendix 5: Review of animal and human studies published since FDA's 2010 assessment of long-chain perfluorocarboxylates
- Appendix 6: Long-Chain Perfluorocarboxylates Removed from Commerce in 2011.
- Appendix 7: Requested Changes to 21 C.F.R. § 176.170

Appendix 1
Responses to Elements Required by 21 C.F.R. § 171.1

Per 21 C.F.R. § 171.1, we provide responses to the requested elements of a food additive petition with one element per page.

Name and Pertinent Information Concerning Food Additive

The identity of the food additive is as follows:

1.	Name:	Long-chain perfluorocarboxylates listed in 21 C.F.R. § 176.170 and described in detail in Appendix 2.
2.	Chemical formula:	Not applicable. Multiple chemicals
3.	Formula weight:	Not applicable. Multiple chemicals
4.	Chemical Abstract Service No.:	Not applicable. Multiple chemicals
5.	INS No.:	Not applicable. Multiple chemicals
6.	UNI No.:	Not applicable. Multiple chemicals

Any chemical listed in 21 C.F.R. § 176.170 and described in detail in Appendix 2 that meets the descriptions for long-chain perfluorocarboxylates.

The composition, raw materials, and manufacturing method are described in the food additive petitions that FDA approved as follows:

- For FAP 5B1747 accepted pursuant to Federal Register Docket No. 67-10113 on August 28, 1967 for "Diethanolamine salts of mono- and bis (1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C8-C18 and the salts have a fluorine content of 52.4% to 54.4% as determined on a solids basis."
- For FAP 3B3700 accepted pursuant to Federal Register Docket No. 83F-0043 on March 4, 1983 and amended on October 26, 1983 for "Pentanoic acid, 4,4-bis [(*gamma-omega*-perfluoro-C8-20-alkyl)thio] derivatives, compounds with diethanolamine (CAS Reg. No. 71608-61-2)."
- For FAP 3B4353 accepted pursuant to Federal Register Docket No. 92F-0504 on January 26, 1993 and amended on July 22, 1995 for "Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma], [omega]-perfluoroC4-20alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide."

Directions, Recommendations, and Suggestions Regarding Proposed Use
We are asking FDA to revoke the approvals for the long-chain perfluorocarboxylates as described in the section above.

Data establishing that food additive will have intended physical or other technical effect.
We are asking FDA to revoke the approvals for the long-chain perfluorocarboxylates as described in the section above. As a result, there is no intended physical or technical effect.

Description of practicable methods to determine the amount of the food additive in the food
We are asking FDA to revoke the approvals for the long-chain perfluorocarboxylates. As a result, there should be no amount of the food additive in the food.

Full reports of investigations made with respect to the safety of the food additive
See Appendices 4 and 5.

Proposed tolerances for the food additive
We are asking FDA to revoke the approvals for the long-chain perfluorocarboxylates as described in the section above. As a result, no tolerance is needed. Appendix 3 describes current estimated exposures for these chemicals.

Full information on each proposed change to the original regulation
See Appendix 7 for the specific changes requested to 21 CFR §176.170. Text in strikethrough font is to be deleted.

Environmental impact statement
This food additive petition is categorically excluded from the need to prepare an Environmental Assessment under 21 CFR 25.32(m) for actions to prohibit or otherwise restrict or reduce the use of a substance in in food, food packaging, or cosmetics. The proposed action complies with the categorical exclusion criteria. No extraordinary circumstances exist which would require the submission of an Environmental Assessment or Environmental Impact Statement.

Appendix 2
Description of each of the three classes of long-chain perfluorocarboxylates

We reviewed 21 C.F.R. § 176.170 and identified three classes of compounds that include chemicals that met this definition. They are as follows:

1. Diethanolamine salts of mono- and bis (1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C8-C18 and the salts have a fluorine content of 52.4% to 54.4% as determined on a solids basis

This class meets the definition of a long-chain perfluorocarboxylates because the perfluoroalkyl group is defined as having a chain with between 8 and 18 carbons. At least some of the chemicals appear to be a precursor of perfluorocarboxylic acid.

In 1967, FDA approved the use of this class of chemicals in response to a food additive petition by E.I. du Pont de Nemours & Company (DuPont).[17] Three years later, the company submitted a food additive petition to reduce these levels by 18% but FDA does not appear to have accepted it.[18]

The regulation allows chemicals that meet this description to be used "only as an oil and water repellant at a level not to exceed 0.17 pound (0.09 pound of fluorine) per 1,000 square feet of treated paper or paperboard, as determined by analysis for total fluorine in the treated paper or paperboard without correction for any fluorine which might be present in the untreated paper or paperboard, when such paper or paperboard is used in contact with nonalcoholic foods . . . ."[19] It may be used in a wide range of conditions excluding only high temperature heat sterilized.

To provide context on these limits, consider the FDA approved maximum application rate of 0.17 pound of the chemical per 1000 ft^2. This corresponds to 77 mg/ft^2. A square foot is a little smaller than a 14" pizza, a sandwich wrapper, or 6" carryout box: common uses for greaseproofing paper and paperboard. Not all of these chemicals in the paperboard would likely get into the food. FDA's regulation sets an upper limit of how much of the chemical may be getting into food at 0.5 mg/in^2.[20] For one square foot, this limit corresponds to 72 mg.

Migration tests conducted by the company demonstrated that the chemical was not likely to migrate into food at levels anywhere near the allowed amount. Based on these tests, FDA concluded that aqueous foods in contact with the treated paper under the range of conditions of use would be below 0.51 ppm.[21] After DuPont submitted additional tests, FDA agreed the rates would be 0.07 ppm for fatty foods and 0.09 for aqueous foods. Since only 5 percent of all food consumed would be in contact with treated paper, the combined impact on diet of 0.0044 ppm.[22]

[17] 32 Fed. Reg. 12,474 (Aug. 29, 1967).
[18] 35 Fed. Reg. 13,323 (Aug. 20, 1970).
[19] 21 C.F.R. § 176.170(b).
[20] 21 C.F.R. § 176.170(c).
[21] FDA Memo dated October 6, 1970.
[22] FDA Memo dated December 8, 1971.

Using FDA's standard assumption of a 3 kg diet, an adult's estimated exposure to the Class 1 perfluorocarboxylates would be 0.013 mg/day.

2. Pentanoic acid, 4,4-bis [(*gamma-omega*-perfluoro-C8-20-alkyl)thio] derivatives, chemicals with diethanolamine (CAS Reg. No. 71608-61-2)

This class meets the definition of a long-chain perfluorocarboxylates because the perfluoroalkyl group is defined as having a chain with between 8 and 18 carbons. At least some of the chemicals appear to be a precursor of perfluorocarboxylic acid.

In 1983, FDA approved the use of this class of chemicals in response to a food additive petition by Ciba-Geigy Corporation.[23]

The regulation allows chemicals that meet this description to be used "only as an oil and water repellent and used at a level not to exceed 8 pounds per ton of the finished paper or paperboard when such paper or paperboard is used in contact with nonalcoholic foods"[24] at room temperature or below or for reheating frozen food.

To provide context on these limits, consider the FDA approved maximum application rate of 8 pounds of the chemical per ton of typical paperboard with a weight of 50 pound per 1000 square foot. This corresponds to 91 mg/ft^2. A square foot is a little smaller than a 14" pizza, a sandwich wrapper, or 6" carryout box: common uses for greaseproofing paper and paperboard. Not all of these chemicals in the paperboard would likely get into the food. FDA's regulation sets an upper limit of how much of the chemical may be getting into food at 0.5 mg/in^2.[25] For one square foot, this limit corresponds to 72 mg.

Migration tests conducted by the company demonstrated that the chemical was not likely to migrate into food at levels anywhere near the allowed amount. Based on these tests, FDA concluded that food in contact with the treated paper under the range of conditions of use would be as below 1.5 ppm.[26] After narrowing the range of allowed uses, with only 10 percent of all food consumed would be in contact with treated paper, the combined impact on diet of 0.018 ppm.[27] Using FDA's standard assumption of a 3 kg diet, an adult's estimated exposure to the Class 1 perfluorocarboxylates would be 0.05 mg/day.[28]

The agency based its decision on two toxicology studies: an oral study designed to determine the dose necessary to kill half the animals and a 30-day, subacute oral study in rats.[29]

[23] 48 Fed. Reg. 51,770 (Nov. 14, 1983).
[24] 21 C.F.R. § 176.170(b).
[25] 21 C.F.R. § 176.170(c).
[26] FDA memo dated February 10, 1983
[27] Ciba Geigy memo to FDA dated September 29, 1983.
[28] FDA Memo dated August 2, 1983
[29] FDA Memo dated August 2, 1983

3. Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma], [omega]-perfluoroC4-20alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide

This class meets the definition of a long-chain perfluorinated compound because the perfluoroalkyl group is defined as having a chain with between 4 and 20 carbons. Because the chemicals in this class contain a thio group and are phosphate ester acids, they are likely a precursor of a PFHxS or a perfluorocarboxylic acid. Chemicals with a perfluoroalkyl group of only 4 or 5 carbons are unlikely to be qualify but given the likelihood that the products of a mixture of different carbon chain lengths, we do not believe it is appropriate to consider them to be short-chain perfluorinated compounds.
In 1995, FDA approved the use of this class of chemicals in response to a food additive petition by Ciba-Geigy Corporation.[30] The company submitted a food additive petition to expand the allowed used in 1996[31] and FDA approved that petition in 1997.[32]

The regulation allows chemicals that meet this description to be used "only as an oil and water repellant at a level not to exceed 0.44 percent perfluoroalkyl actives by weight of the finished paper and paperboard in contact with non-alcoholic foods"[33] for frozen or refrigerated storage.

To provide context on these limits, consider the FDA approved maximum application rate of 8 pounds of the chemical per ton of typical paperboard with a weight of 50 pound per 1000 square foot. This corresponds to 100 mg/ft^2. A square foot is a little smaller than a 14" pizza, a sandwich wrapper, or 6" carryout box: common uses for greaseproofing paper and paperboard. Not all of these chemicals in the paperboard would likely get into the food. FDA's regulation sets an upper limit of how much of the chemical may be getting into food at 0.5 mg/in^2.[34] For one square foot, this limit corresponds to 72 mg.

Migration tests conducted by the company demonstrated that the chemical was not likely to migrate into food at levels anywhere near the allowed amount. Based on these tests in Ciba-Geigy's petition to expand the uses, FDA concluded that food in contact with the treated paper under the range of conditions of use would be as below 0.52 ppm. [35] With only 8 percent of all food consumed would be in contact with treated paper, the combined impact on diet of 0.04 ppm.[36] Using FDA's standard assumption of a 3 kg diet, an adult's estimated exposure to the Class 1 perfluorocarboxylates would be 0.13 mg/day.[37]

[30] 60 Fed. Reg. 39,645 (Aug. 3, 1995).
[31] 61 Fed. Reg. 37,483 (July 18, 1996).
[32] 62 Fed. Reg. 10,452 (Mar. 7, 1997).
[33] 21 C.F.R. § 176.170(b).
[34] 21 C.F.R. § 176.170(c).
[35] FDA Memo dated August 30, 1996.
[36] FDA memo dated January 14, 1997.
[37] Ibid.

Appendix 3
FDA's related estimated daily intakes for perfluorocarboxylates

According to FDA's "List of Indirect Additives Used in Food Contact Substances" database, of the 3,237 chemicals in the database, 1000 are authorized by 21 C.F.R. § 176.170 to be used to treat paper and paperboard in contact with aqueous and fatty foods.[38] From this list of 1000, we identified 9 that were perfluorocarboxylates. See Table A3-1.

For several of the chemicals, we were not able to determine the class as described in Appendix 2 since the number provided in the database was not an actual CAS number but instead was assigned by FDA and the names were difficult to match. Where we could make the connection based on name or CAS number, we designated the class in the third column.

When we look at the carbon chain lists for the first four (FDA Doc. No. 7100, 7101, 7102, and 7088), they include chains as short as two carbons. Nowhere in 21 C.F.R. § 176.170 can we see where these are allowed. It appears that FDA's publicly available database identified chemicals as authorized by that section when in fact they are not covered. We do not know how to resolve this contradiction.

Table A3-1: Long-chain perfluorocarboxylates in FDA's Indirect Additives Database

Chemical Name*	CAS No. or FDA ID No.**	Class (from Appendix 2)
TETRAAMMONIUM2,2-BIS(**PERFLUOROALKYL(C2-18)**ETHYL)THIOMETHYL)-1,3-BIS(DIHYDROGENPHOSPHATE)PROPANE	977169-41-7 FDA Doc No. 7100	Unknown
DIAMMONIUM2,2-BIS((**PERFLUOROALKYL(C2-18)**ETHYL)THIOMETHYL)-3-HYDROXYPROPYL PHOSPHATE	977169-40-6 FDA Doc No. 7101	Unknown
AMMONIUMBIS(2,2-BIS((**PERFLUOROALKYL(C2-18)**ETHYL)THIOMETHYL)-3 HYDROXYPROPYL)PHOSPHATE	977169-39-3 FDA Doc No. 7102	Unknown
AMMONIUM5,5-BIS((**PERFLUOROALKYL(C2-18)**ETHYL)THIOMETHYL)-2-HYDROXY-2-OXO-1,3,2-DIOXAPHOSPHORINANE	977169-38-2 FDA Doc No. 7088	Unknown
DIETHANOLAMINEMONO- AND BIS(1H,1H,2H,2H-**PERFLUOROALKYL**) PHOSPHATE	977042-24-2 FDA Doc No. 5436	1
PENTANOICACID, 4,4-BIS ((GAMMA-OMEGA-**PERFLUORO-C8-20-ALKYL)**THIO) DERIVATIVES,COMPOUNDS WITH DIETHANOLAMINE	71608-61-2 FDA Doc No. 5171	2
* Portions of the chemical name indicating it is a long-chain perfluorinated chemical in bold typeface. **Numbers that begin with 977 were assigned by FDA and are not Chemical Abstract Service (CAS) numbers.		

[38] FDA, List of Indirect Additives Used in Food Contact Substances, http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=176.170&sortColumn=&rpt=iaListing (accessed March 11, 2014).

In FDA's Cumulative Estimated Daily Intake (CEDI) Database,[39] we found exposure estimates for long-chain perfluorocarboxylates. See Table A3-2. We sorted them by decreasing estimated daily intake. Because of differences in FDA's naming chemicals and FDA assignment of its own numbers instead of proper CAS numbers, it is difficult to connect these chemicals to the three classes in Table 1 that are described in 21 C.F.R. § 176.170. Where we could make the connection based on name or CAS number, we designated the class after the C.F.R section number cited (last column).

FDA's publicly accessible resources regarding the database do not explain specifically how the agency developed its estimates.

Table A3-2: Long-chain perfluorocarboxylates in FDA's Cumulative Estimated Daily Intake (CEDI) database

Chemical Name in FDA's Database[1]	CAS No. or FDA ID No.[2]	CUM DC (ppb)[3]	CEDI (mg/kg-bw/day)[4]	21 CFR Section Cited[5]
PENTANOIC ACID, 4,4-BIS ((GAMMA-OMEGA-**PERFLUORO-C8-20-ALKYL**)THIO) DERIVATIVES, COMPOUNDS WITH DIETHANOLAMINE	71608-61-2	18	0.0009	176.170 Class 1
PERFLUOROALKYL SUBSTITUTED PHOSPHATE ESTER ACIDS, AMMONIUM SALTS FORMED BY REACTION OF 2,2-BIS[(GAMMA,OMEGA-**PERFLUORO-C(4-20)**-ALKYLTHIO)METHYL]-1,3-PROPANEDIOL, POLYPHOSPHORIC ACID AND AMMONIUM HYDROXIDE	None provided by FDA	15.5	0.000775	176.170 Class 3
AMMONIUM BIS(2,2-BIS((**PERFLUOROALKYL**(C2-18)ETHYL)THIOMETHYL)-3 HYDROXYPROPYL) PHOSPHATE	977169-39-3	8	0.0004	176.170 Class 3
COPOLYMERS OF 2-**PERFLUOROALKYL**ETHYLACRYLATE, 2-N,N-DIETHYLAMINOETHYL METHACRYLATE, AND GLYCIDYL METHACRYLATE	None provided by FDA	7	0.00035	None Listed
2-**PERFLUOROALKYL**ETHYL ACRYLATE	65605-70-1	1.4	0.00007	None Listed
COPOLYMERS OF 2-**PERFLUOROALKYL**ETHYLACRYLATE, 2-N,N-DIETHYLAMINOETHYL METHACRYLATE, AND GLYCIDYL METHACRYALTE	247047-61-6	1.1	0.000055	None Listed
BIS(1,1,2,2-TETRAHYDRO**PERFLUOROOCTYL**) ETHER	78522-74-4	0.58	0.000029	None Listed

[39] FDA, CEDI Database, http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm (accessed March 2, 2014)

2-PROPENOIC ACID, 2-METHYL-, 2-(DIMETHYLAMINO)ETHYL ESTER, POLYMERS WITH 2-GAMMA-OMEGA-**PERFLUORO-C(8-14)**-ALKYL ACRYLATE, ACETATES, N-OXIDES	479029-28-2	0.5	0.000025	None Listed
PERFLUOROOCTANOIC ACID	335-67-1	0.12	0.000006	None Listed
TERPOLYMER OF TETRAFLUOROETHYLENE, **PERFLUORO(2,5-DIMETHYL-3,6-3,6-DIOXANONANE** VINYL ETHER, AND PERFLUORO(6,6-DIHYDRO-6-IODO-3-OXA-1-HEXENE)	106108-23-0	0.05	0.0000025	None Listed

[1] Portions of the chemical name indicating it is a long-chain perfluorocarboxylate in bold typeface.
[2] Numbers that begin with 977 were assigned by FDA and are not Chemical Abstract Service (CAS) numbers.
[3] CUM DC = Dietary concentration in the food expressed in parts per billion (pbb)
[4] CEDI = Cumulative estimated daily intake determined by FDA's Office of Food Additive Safety (OFAS) for the food contact substance in mg of chemical per kilogram of body weight per day (mg/kg bw/d).
[5] Where we could match the chemical named in CEDI with one of the three classes in Table 1, we noted the match.

We also evaluated four additional resources for exposure information on long-chain perfluorinated compounds. First, in 2009, the Centers for Disease Control and Prevention (CDC) released its Fourth National Report on Human Exposure to Environmental Chemicals.[40] CDC has updated the information with more recent test results at http://www.cdc.gov/exposurereport/. The report describes serum test results from the National Health and Nutrition Examination Survey's (NHANES) biomonitoring for the following long- and short-chain perfluorochemicals:

- Perfluorobutane Sulfonic Acid (PFBuS)
- Perfluorodecanoic Acid (CAS. No. 335-76-2) (PFDeA)
- Perfluorododecanoic Acid (CAS No. 307-55-1) (PFDoA)
- Perfluoroheptanoic Acid (CAS No. 375-85-9) (PFHpA)
- Perfluorohexane Sulfonic Acid (CAS No. 355-46-4) (PFHxS)
- Perfluorononanoic Acid (CAS No.375-95-1) (PFNA)
- Perfluorooctanoic Acid (CAS No. 335-67-1) (PFOA)
- Perfluorooctane Sulfonic Acid (CAS No. 1763-23-1) (PFOS)
- Perfluorooctane Sulfonamide (CAS No. 754-91-6) (PFOSA)
- 2-(*N*-Ethyl-Perfluorooctane sulfonamide) Acetic Acid (Et-PFOSA-AcOH)
- 2-(*N*-Methyl-perfluorooctane sulfonamido) Acetic Acid (Me-PFOSA-AcOH)
- Perfluoroundecanoic Acid (CAS No. 2058-94-8) (PFUA)

The monitoring results show that many Americans have been exposed to at least one of these 12 chemicals or one of the chemical's precursors.

Perfluorocarboxylates approved by FDA in 21 C.F.R. § 176.170 (the three classes described in Table 1) may be metabolized into some of the chemicals monitored by NHANES. More

[40] CDC, Fourth National Report on Human Exposure to Environmental Chemicals, 2009. See http://www.cdc.gov/exposurereport/ started at page 247.

information would be needed about the specific chemicals used and how they are metabolized to make a firm determination.

Second, the European Food Safety Authority (EFSA) also has conducted a series of progressively more detailed exposure studies for long-chain perfluorinated compounds. In 2008, it published a preliminary evaluation and developed a tolerable daily intake.[41] In 2012, it issued a more detailed examination of the levels in food.[42]

Third, in 2013, the European Commission's Community Research and Development Information Service published its final report for its project titled PERFluorinated Organics in Our Diet (PERFOOD).[43] This report describes tools to monitor the chemicals in food and drinking water. It also provides the results of studies looking at the impact of food contact materials and process technologies including some migration studies.

These European studies may be difficult to connect to FDA's CEDI because Europe's allowed uses of long-chain perfluorocarboxylates cannot be easily compared to those allowed by FDA pursuant to 21 C.F.R. § 176.170 or the chemicals named in CEDI.

Fourth, in 2010 Schecter et al. reported on the presence of perfluorocarboxylates in composite food samples.[44] The study showed perfluorooctanoic acid (PFOA) was measured in 17 of 31 samples, ranging from 0.07 ng/g in potatoes to 1.80 ng/g in olive oil. Two years later, the same lead author found that perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS), and perfluorooctane sulfonic acid (PFOS), were detected in the blood of > 92% of 300 participating children; the other PFCs measured were detected less frequently. Overall median serum concentrations of PFOS (4.1 ng/mL) were higher than those for PFOA (2.85 ng/mL), PFNA (1.2 ng/mL), and PFHxS (1.2 ng/mL).[45]

[41] EFSA, Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts: Scientific Opinion of the Panel on Contaminants in the Food chain (Question No EFSA-Q-2004-163), 2008, The EFSA Journal, (2008) 653, 1-131

[42] EFSA, Scientific Report of EFSA, Perfluoroalkylated substances in food: occurrence and dietary exposure, 2012, EFSA Journal 2012:10(6):2743.

[43] CORDIS, PERFOOD Scientific and Technological Results, 2013. See http://cordis.europa.eu/publication/rcn/15158_en.html.

[44] Schecter et al., Perfluorinated Compounds, Polychlorinated Biphenyls, and Organochlorine Pesticide Contamination in Composite Food Samples from Dallas, Texas, USA, 2010, *Environ Health Perspect* 118:796-802 (2010). http://dx.doi.org/10.1289/ehp.0901347.

[45] Schecter et al., Polyfluoroalkyl Compounds in Texas Children from Birth through 12 Years of Age, 2012, *Environ Health Perspect*; DOI:10.1289/ehp.1104325.

Appendix 4
Toxicology assessment for three classes of long-chain perfluorocarboxylates

FDA's 2010 toxicological assessment of long-chain perfluorocarboxylates[46] is incorporated by reference. To update that assessment, the Natural Resources Defense Council (NRDC) took a five-step approach to identifying the available toxicology literature relevant to the three classes of long-chain perfluorocarboxylates whose approval at 21 CFR 176.170 NRDC seeks to have the Food and Drug Administration (FDA) revoke. The three classes are described in Table 1 and listed below for convenience:

Class 1: Diethanolamine salts of mono- and bis (1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C8-C18 and the salts have a fluorine content of 52.4% to 54.4% as determined on a solids basis

Class 2: Pentanoic acid, 4,4-bis [(*gamma*-*omega*-perfluoro-C8-20-alkyl)thio] derivatives, chemicals with diethanolamine (CAS Reg. No. 71608-61-2)

Class 3: Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma], [omega]-perfluoroC4-20alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide

NRDC took a five-step approach to review information available to us for the three classes.

Step 1: *Review food additive petition documents.* We reviewed the *Federal Register* notices for the food additive petitions addressing the three classes of long-chain perfluorocarboxylates as well as documents developed by FDA as part of its review of the petitions that the agency provided to us.

Step 2: *Review published literature for the three classes of long-chain perfluorocarboxylates.* We conducted a comprehensive review of the literature to identify toxicology studies for the three classes of chemicals.

Step 3: *Review FDA's 2010 toxicology assessment of long-chain perfluorocarboxylates.* We reviewed the toxicology assessment[47] provided by FDA conducted in 2010 by its food additive toxicologists. The analysis concluded that until additional data gaps are filled, long-chain perfluorocarboxylates should be considered as a class of chemicals associated with cancer and adverse effects on pre- and post-natal development and on reproductive health and function. The three classes of chemicals addressed in this food additive petition would qualify in the broader class of long-chain perfluorocarboxylates.

Step 4: *Review EPA's 2014 draft health assessment of PFOA and its precursors*. In February, 2014, the Environmental Protection Agency's drinking water

[46] FDA Memo from Toxicology Group I to Regulatory Group 2 on September 30, 2010 at page 34-35.
[47] *Ibid.*

program released a comprehensive health assessment of PFOA and its precursors. These precursors included the three classes of long-chain perfluorocarboxylates addressed in this food additive petition. The agency sought public comment on the report and solicited nominations for an external peer review panel that will review the report in detail. We reviewed EPA's assessment and identified studies referenced by EPA and published after 2009 and not included in the FDA's analysis.

Step 5: *Review public comments on EPA's draft health assessment of PFOA and its precursors.* As part of its request for public comments on its February 2014 health assessment, EPA also asked for suggestions on additional studies that it and the external peer review panel should consider. When the comment period closed and the comments were posted at www.regulations.gov, we reviewed them to identify issues and identified additional studies not referenced by FDA in 2010 or by EPA in 2014.

Appendix 5 describes our analysis of the 10 animal studies and includes the latest published scientific evidence that PFOA is "known to be toxic" to human reproduction and development we identified through this process published after 2009 that were not considered in FDA's 2010 toxicological assessment of long-chain perfluorocarboxylates.

Step 1: Review food additive petition documents.
We reviewed the following *Federal Register* notices related to the food additive petitions for the three classes:

- Class 1
  - 32 Fed. Reg. 12474 (August 29, 1967)
  - 35 Fed. Reg. 13323 (August 20, 1970)
- Class 2
  - 48 Fed. Reg. 11513 (March 18, 1983)
  - 48 FedReg 51770 (November 14, 1983)
- Class 3
  - 58 Fed. Reg. 8289 (February 12, 1993)
  - 60 Fed. Reg. 39625 (August 3, 1995)
  - 61 Fed. Reg. 37351 (July 18, 1996)
  - 62 Fed. Reg. 10411 (March 7, 1997)

None of the notices referred to any hazard characterization, hazard identification or toxicology studies.

Of the redacted documents that FDA provided NRDC for each of the three classes, we identified the following references to hazard characterization, hazard identification or toxicology studies:

- Class 2: FDA said that "This conclusion is based on 'virtually nil' migration, oral LD50 studies in animals, and a 30-day subacute oral study in rats."[48]

[48] FDA Memo from Quinn to Director of Foods on August 2, 1983 recommending approval of additive.

- Class 3: FDA said that "The DHEE representative concludes that based on the 'virtually nil' dietary exposure to the additive, the proposed use of the subject additive is supported by the available toxicity data presented in the petition."[49]

In summary, it is unlikely that the studies would be sufficient to determine whether the adverse effects described in FDA's 2010 assessment of long-chain perfluorocarboxylates were occurring with these classes of chemicals.

Step 2: Review published literature for the three classes of long-chain perfluorocarboxylates

While FDA's 2010 assessment[50] consider long-chain perfluorocarboxylates as a class, it is not clear from the documentation whether the agency specifically searched for the three classes of perfluorocarboxylates covered by this petition and described in Table 1. Therefore, NRDC conducted a literature search for the three classes following FDA's format and using the same resources listed by the agency: the U.S. EPA's website, the Agency for Toxic Substances and Disease Registry (ATSDR)'s website, PubMed, Google Scholar, ToxNet, ChemIDplus advanced, Scirus, and IPCS Inchem. Our objective was to identify relevant animal studies whether published before or after 2010. Because FDA's description of the classes at 21 CFR § 176.170 contain descriptive words in addition to chemical terms, we distilled the classes into the following search terms to help ensure our review was broad:

- Class 1:
  - Diethanolamine salts of mono- and bis(1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates
  - 1H,1H,2H,2H perfluoroalkyl phosphates
- Class 2:
  - 71608-61-2
  - Pentanoic acid, 4,4-bis [(*gamma-omega*-perfluoro-C8-20-alkyl)thio]
  - 4,4-bis [(gamma-omega-perfluoro-C8-20-alkyl)thio]
- Class 3:
  - 2,2-bis[([gamma], [omega]-perfluoroC4-20alkylthio) methyl]-1,3-propanediol
  - Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma], [omega]-perfluoroC4-20alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide

a. **U.S. EPA's website**: We found that in 2006 the agency revoked a tolerance exemption for chemicals similar to Class 1[51] as part of its systematic review of active and 'inert' ingredients in pesticides pursuant to the Food Quality Protection Act of 1996. The class was described as "Mono- and Bis-(1*H*, 1*H*, 2*H*, 2*H*-perfluoroalkyl) Phosphates Where the Alkyl Group is Even Numbered and in the C6-C12 Range." The only difference from Class 1 is in the carbon chain length: Class 1 includes C8 to C18 while EPA considered C6 to C12. In light of FDA's conclusion that longer chain lengths are more likely to persist in the human body, they may be more potent that the ones revoked by EPA.

[49] FDA Memo from Rulis to Director of Center for Food Safety and Applied Nutrition on January 14, 1997 recommending approval of additive.
[50] FDA Memo from Toxicology Group I to Regulatory Group 2 on September 30, 2010 at page 34-35.
[51] 71 *Fed.Reg.* 45408 (August 9, 2006).

By revoking the tolerance exemption, EPA concluded that it could not be reasonably certain that the intended use would cause no harm and prohibited the use of the chemicals in pesticides. Three companies commented on EPA's notice. None challenged EPA's conclusions on the chemical described under the current tolerance exemption. The agency concluded that:

> "EPA determined that there were potential risks of concern associated with the use of these perfluoroalkyl phosphates. EPA concluded that it was unable to determine that the tolerance exemption met the safety requirements of FFDCA section 408(c)(2) and proposed the revocation of the tolerance exemption in the **Federal Register** on April 19, 2006 (71 FR 20048) (FRL–8058–3).

b. **National Institute of Health's ChemID*plus***: We only found information for Class 2 search terms.[52] It was described in three EPA databases: TSCA Inventory, ACToR, and SRS. We checked each of those databases and found only descriptions of the chemicals and no evidence of toxicology studies.

c. **National Library of Medicine's PubMed**: We found four studies for perfluorinated compounds: three systematic reviews on PFOA and a cross-sectional study using NHANES data from 1999-2008. The systematic reviews were:

- To determine whether developmental exposure to PFOA affects fetal growth hormone.[53] After applying a rigorous and transparent method to evaluate epidemiological data, the authors reviewed 18 human studies and found that a 1 ng/ml increase in serum or plasma PFOA was associated with a -18.9 g difference in birth weight. They concluded that "there is "sufficient" human evidence that developmental exposure to PFOA reduces fetal growth."
- To answer whether fetal developmental exposure to PFOA or its salts affect fetal growth in animals.[54] After applying a rigorous and transparent method to evaluate animal data, the authors reviewed 21 studies that met their criteria. They found that increased dams exposure concentration of PFOA was associated with decreased pup birth weight (-0.023 g per 1-unit increase in dose (milligram/kilogram body weight-day)). They concluded that there was sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.
- To integrate scientific findings from human and animal studies to determine the overall strength of the evidence to answer the question: does developmental

[52] http://chem.sis.nlm.nih.gov/chemidplus/rn/71608-61-2.

[53] Johnson PI et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1028-1039. http://dx.doi.org/10.1289/ehp.1307893

[54] Koustas E et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1015-1027. http://dx.doi.org/10.1289/ehp.1307177

> exposure to PFOA affect fetal growth in humans.[55] The integration of human and animal data "produced a final strength of evidence rating in which the review authors concluded that PFOA is "known to be toxic" to human reproduction and development." The authors concluded that "developmental exposure to PFOA adversely affects human health."

The cross sectional study evaluated the association between serum concentration of eight PFCs, including PFOA, PFOS, PFNA and PFHxS, with self-reported lifetime asthma, wheezing and current asthma among 12-19 years of age NHANES participants.[56] They concluded that the study "provides some evidence for associations between exposure to PFCs and asthma-related outcomes in children."

Summarizing Step 2, only one of the resources used by FDA (PubMed) revealed studies for a handful of perfluorinated carboxylates; none of the resources revealed any studies for the three classes of chemicals. Abstracts of the studies are included in Appendix 5.

Step 3: Review FDA's 2010 toxicology assessment of long-chain perfluorcarboxylates

In 2010, the U.S. Food and Drug Administration's (FDA) food additives toxicologists updated a series of reviews they had conducted of long-chain perfluorinated compounds.[57] A 2002 review had set a unit risk cancer value for perfluorooctanoic acid (PFOA).[58] A 2007 review found that "carcinogenicity was considered to be the most sensitive and relevant endpoint for PFOA in particular."[59] The 2010 review focused on three non-cancer endpoints: pre- and post-natal development; reproductive health and function; and thyroid gland.

Much of the toxicology and epidemiology research has focused on PFOA because long-chain perfluorinated chemicals may be degraded into PFOA in the environment. However FDA's scientists concluded that they are not metabolized to PFOA in the body.[60] Because PFOA is structurally similar to many types of long-chain perfluorinated compounds, especially carboxylates, the agency used evidence of PFOA and other similar chemicals to identify similar data gaps for those it reviewed for safety.

In sum, the agency's food additive toxicologists reached the following conclusions for perfluorinated compound with long chains (e.g. chains of at least eight carbons saturated with fluorine).

---

[55] Robinson KA et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1040-1051. http://dx.doi.org/10.1289/ehp.1307923

[56] Humblet O et al. Perfluoroalkyl Chemicals and Asthma among Children 12–19 Years of Age: NHANES (1999–2008). 2014. *Environmental Health Perspectives* 122:1129-1133. http://dx.doi.org/10.1289/ehp.1306606

[57] FDA Memo from Toxicology Group I to Regulatory Group 2 on September 30, 2010 at page 34-35.

[58] *Ibid*., p. 1 citing Twaroski/Gilliam, 10/1/02.

[59] *Ibid*., citing McDougal/Honigfort, 6/13/07.

[60] *Ibid.*, p. 4. Note that this conclusion is inconsistent with statements by the Agency for Toxic Substances and Disease Registry in 2009 as part of its draft toxicological profile on perfluoroalkyls. ATSDR stated that "[e]xposure of mice to 8– 2 telomer alcohol also generated PFNA [perfluorononanoic acid] as a metabolite (Kudo et al. 2005)." [ATSDR 2009 page 226]

- **Cancer:** "In the absence of data to suggest otherwise, carcinogenicity was also considered to be the most sensitive endpoint for structurally-similar perfluorinated compounds, such as ≥ C8 perfluorinated telomer alcohols, based on the available data for PFOA. . . ."[61]
- **Pre- and post-natal development:** The toxicologists found perfluorocarboxylic acids and perfluorotelomer alcohols have adverse effects for the following parameters:
    - Pregnancy maintenance/fetal loss;
    - Reduced skeletal ossification and/or skeletal variations;
    - Decreased fetal body weight;
    - Neonatal survival;
    - Decreased post-natal bodyweight gain prior to weaning;
    - Delayed attainment of eye-opening and hair growth; and
    - Stunted mammary gland development in animals exposed during gestation.[62]
- **Reproductive health and function:** The toxicologists found perfluorocarboxylates have adverse effects for the following parameters:
    - Fertility and estrous cycle parameters;
    - Ovarian and accessory sex organ weight parameters;
    - Ovarian and/or accessory sex organ histopathology; and
    - Serum hormones.[63]
- **Thyroid gland:** The toxicologists found that the reviewed evidence for perfluorinated compounds on thyroid function was mixed.[64]

The scientists noted that "[w]hile the available data on the developmental effects of ≥C8 perfluorinated compounds is scarce, the known increase in biopersistence, and hence potency, supports the generalization of the results from the C8 homologues to the entire class."[65]

The scientists made clear that there is considerable uncertainty with regard to the effects of long-chain perfluorinated compounds as a class due to factors that include:

- Almost all of the available data are from studies conducted with PFOA; lack of information on the pharmacokinetics of long-chain perfluorocarboxylic acids and the eight-carbon, telomer-based perfluorinated alcohols in species other than rats;
- Lack of information on the pharmacokinetics of the telomer-based perfluorinated alcohols longer than eight carbons; and
- Paucity of toxicity data appropriate for use in human health risk assessment for perfluorocarboxylic acids and perfluorinated telomer alcohols with more than eight carbons.[66]

Based on its analysis, FDA's food additive toxicologists recommended "a full, Redbook-compliant, one-year study with an *in utero* phase, as this study design will provide the most comprehensive assessment of the endpoints of concern. This study design will assess chronic toxicity and the possibility of delayed toxicity in adulthood derived from developmental

[61] *Ibid.*, p. 1 citing McDougal/Honigfort, 6/13/07.
[62] *Ibid.*, p. 16-17.
[63] *Ibid.*, p. 30-31.
[64] *Ibid.*, p. 33.
[65] *Ibid.*, p. 34-35.
[66] *Ibid.*, p. 35.

exposure, as well as assessing effects on the developing and mature endocrine system. Moreover, as per the discussion above regarding the appropriate model for use in risk assessment of these compounds, Toxicology recommends that the one-year study with *in utero* phase be conducted in mice, due to pharmacokinetic considerations."[67]

Summarizing Step 3, NRDC believes that the three classes of perfluorocarboxylates in Table 1 should be treated as a class with other perfluorocarboxylates including PFOA.

Step 4: Review EPA's 2014 draft health assessment of PFOA and its precursors

In February 2014, the U.S. Environmental Protection Agency's (EPA) Drinking Water Program released its draft comprehensive assessment of the health effects of PFOA.[68] Because carboxylates degrade in the environment into PFOA, the analysis considered the science involving those chemicals as well. The agency stated that "PFOA is not readily eliminated from humans as evidenced by the half-life of 2.3 years. In contrast, half-life values for the monkey, rat, and mouse are 20.8 days, 11.5 days, and 15.6 days, respectively. Differences in transporters may explain species differences in elimination."[69] It found a positive association between:

- Serum PFOA concentrations and:
    - Increased liver enzymes and/or decreased bilirubin in both worker and general populations;
    - Chronic kidney disease in the general population, and
    - Odds of experiencing early menopause.
- Maternal or child plasma levels of PFOA and:
    - Decreased antibody titers in children after vaccination;
    - Obesogenic effects in female children at 20 years of age; and
    - Parent reported Attention Deficit Hyperactivity Disorders.[70]

Based on this data, EPA selected a draft ingestion reference dose (RfD) for PFOA of 0.00002 mg/kg-bw/day (equivalent to 20 nanograms/kg-bw/day).[71]

If, as FDA concluded in 2010, perfluorocarboxylates are a class that includes PFOA, then this RfD should be applied to all perfluorocarboxylates including the three classes in Table 1. Since the longer chain perfluorocarboxylates are likely to be retained in the body at greater levels than PFOA, the RfD may need to be lower. Only additional toxicology data from the type of study FDA's toxicologists called for in 2010, would be able to rebut this presumption.

EPA developed potential RfDs ranging from 0.000003 to 0.00002 mg/kg-bw/day after systematically examining the toxicology and applying appropriate uncertainty factors using:

- No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) values;
- Lower 90% confidence bounds on the Benchmark Dose Level ($BMDL_{10}$); and

[67] *Ibid.*
[68] EPA, DRAFT Health Effects Documents for Perfluorooctanoic Acid (PFOA), EPA Doc. No. 822R14001, 2014.
[69] *Ibid.*, p. 1-1.
[70] *Ibid.*
[71] *Ibid.*, p. 1-2.

- Human Equivalent Dose (HED) based on the NOAEL and LOAEL.[72]

The agency selected 0.00002 mg/kg-bw/day as the draft RfD because it was the most commonly occurring RfD; however, it was almost 7 times greater than the lowest one calculated. The agency reasoned that:

> "This value is the outcome for all modeled rat and mouse serum values except for the Dewitt et al. (2008) 15-day study with an impact on liver weight but not the co-monitored immunological effects. The liver endpoint in the Lau et al. (2006) and York et al. (2002) studies were accompanied by developmental effects and effects on kidney weights, respectively. The modeled serum value from Thumford (2001) based on liver effects in the monkey, also strongly supports the chosen RfD." [73]

EPA's evaluation builds on three other evaluations. In an October 28, 2009 memo, EPA's Office of Emergency Management and its Office of Superfund Remediation and Technology Innovation jointly developed RfDs for PFOA and PFOS for use in clean-up situations.[74] This document was based on January 2009 provisional health advisories (PHAs) developed by EPA's Office of Water. The PHAs relied heavily on the European Food Safety Authority's (EFSA) 2008 evaluation developing a Tolerable Daily Intake (TDI).[75] The process to develop a TDI is comparable to both EPA's RfD and FDA's ADI.

Natural Resources Defense Council (NRDC) reviewed the bibliography listed in EPA's draft assessment and found 56 references not included in FDA's analysis that were published in 2010 or later. Of these 56 references, we found:

- 26 described epidemiology studies;
- 10 described *in vivo* animal studies with 3 on rats and 8 on mice;
- 8 described *in vitro* studies;
- 3 were reviews;
- 2 described human clinical studies;
- 2 described measurement methods;
- 4 described models; and
- 1 described water treatment methods.

We reviewed the 10 *in vivo* animal studies. These are described and discussed in Appendix 5. In summary, NRDC did not find anything in the 10 *in vivo* animal studies that contradicted FDA's conclusions, especially that perfluorocarboxylates should be treated as a class. On the contrary, we found additional evidence supporting FDA's conclusion that these chemicals cause adverse health effects in animals.

---

[72] *Ibid.*, p. 5-19-20. See Table 5-11 and 5-12.
[73] *Ibid.*
[74] EPA, The Toxicity of Perfluorooctanic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS), October 28, 2009. See http://www.epa.gov/opptintr/pfoa/pubs/Final%20PFOA%20PFOS%20RfD%20memo%2010-28-09.pdf.
[75] EFSA, Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts: Scientific Opinion of the Panel on Contaminants in the Food chain (Question No EFSA-Q-2004-163), 2008, The EFSA Journal, (2008) 653, 1-131.

Step 5: Review public comments on EPA's draft health assessment of PFOA and its precursors

When EPA released its draft health assessment for PFOA in February 2014, it sought public comments on the document seeking, in particular, information on additional studies it should consider.[76] It also asked for nominations for an external peer review panel.[77] Two months later, the agency posted the responses to its request for comments[78] and announced its interim list of potential peer reviewers and sought comments on the list.[79]

NRDC reviewed the 19 comments EPA received in response to its request. Nine were from industry, five from a state agency, two from academia, and one each from Department of Defense, a law firm representing concerned citizens, and an anonymous individual.

The public comments to EPA identified 89 additional studies addressing PFOA or its precursors not included in EPA 2014 assessment or FDA's 2010 assessment. Of these 89 references, we found:

- 58 described epidemiology studies;
- 14 were reviews;
- 6 described human clinical studies;
- 5 described *in vitro* studies;
- 4 described models.
- 2 described measurement methods;
- 4 described models;
- 0 described *in vivo* animal studies.

Therefore, in Step 5 we identified no additional *in vivo* animal studies conducted on PFOA or perfluorocarboxylates through our review of responses to EPA's request for comments on its health assessment of PFOA or its precursors.

Summary

Overall, after completing the five steps and reviewing the literature[80] published since FDA reached its conclusions that there was insufficient scientific data supporting the safety of long-chain perfluorocarboxylates, the Natural Resources Defense Council (NRDC) found that the evidence of adverse health effects caused by these chemicals has only strengthened since 2010. Although this is a positive finding, a significant gap remains in the toxicology data for the three chemical classes. Therefore, there is no reasonable certainty that the intended uses cause no harm.

[76] 79 Fed.Reg 11429 (February 28, 2014). See also http://peerreview.versar.com/epa/pfoa/.
[77] *Ibid.*
[78] EPA, Docket No. EPA–HQ–OW–2014–0138. See www.regulations.gov.
[79] 79 Fed.Reg. 24419 (April 30, 2014).
[80] See Appendix 4 and 5 for review.

Appendix 5

Review of animal studies published since FDA's 2010 assessment of long-chain perfluorocarboxylates

The following is the Natural Resources Defense Council's analysis of the 10 animal studies, eight on mice and three on rats, not included in FDA's 2010 assessment of perfluorocarboxylates. All 10 studies were located in Step 4 of our analysis where we reviewed EPA's 2014 assessment of PFOA and its precursors.

Mice Toxicology Studies

1. Albrecht, P.P., N.E. Torsell, P. Krishnan, D.J. Ehresman, S.R. Frame, S.-C. Chang, J.L. Butenhoff, G.L. Kennedy, F.J. Gonzalex, and J.M. Peters. 2013. A species difference in the peroxisome proliferator-activated receptor α-dependent response to the developmental effects of perfluorooctanoic acid. Toxicol. Sci. 131: 568-582.
    a. ABSTRACT: This study examined the effect of prenatal perfluorooctanoic acid (PFOA) administration on pre- and postnatal development using peroxisome proliferator-activated receptor α (PPARα)-humanized mice to determine if species differences in receptor activity might influence the developmental effects induced by PFOA. Pregnant mice were treated daily with water or PFOA (3mg/kg) by po gavage from gestation day 1 (GD1) until GD17 and then either euthanized on GD18 or allowed to give birth and then euthanized on postnatal day 20 (PND20). No changes in average fetal weight, crown-to-rump length, or placental weight were observed on GD18. Expression of mRNA encoding the PPARα target genes acyl CoA oxidase (Acox1) and cytochrome P450 4a10 (Cyp4a10) in maternal and fetal liver was increased on GD18 in wild-type and PPARα-humanized mice but not in Pparα-null mice. On PND20, relative liver weight was higher in wild-type mice but not in Pparα-null mice or PPARα-humanized mice. Hepatic expression of Acox1 and Cyp4a10 mRNA was higher in wild-type mice but not in Pparα-null mice or PPARα-humanized mice on PND20. The percentage of mice surviving postnatally was lower in wild-type litters but not in litters from Pparα-null mice or PPARα-humanized mice. No changes in pup weight gain, onset of eye opening, or mammary gland development were found in any genotype. Results from these studies demonstrate that the developmental/postnatal effects resulting from prenatal PFOA exposure in mice are differentially mediated by mouse and human PPARα.
    b. ANALYSIS: This study was conducted in mice using a single dose of PFOA (3mg/kg/day) administered to dams via gavage. Exposure occurred during gestation days (GD) 1 to 17; offspring were evaluated before birth (GD18) or on postnatal day (PND) 20. The study aimed at evaluating whether PPAR alpha may influence the developmental effects induced by PFOA. The study used three different mice: wild type, PPAR alpha-humanized mice and PPAR alpha null mice. Changes in liver gene expression and postnatal survival seem to be differentially mediated by mouse and human PPAR alpha.
    c. CONCLUSION: Unlike the studies cited in FDA's toxicology analysis, this study did not report effects on the mammary gland. This difference is likely due to differences

in doses and age of the offspring. In sum, this study does not contradict FDA's toxicology conclusions regarding prenatal and postnatal endpoints.

2. Li, Y., D.H. Ramdhan, H. Naito, N. Yamagishi, Y. Ito, Y. Hayashi, Y. Yanagiba, A. Okamura, H. Tamada, F.J. Gonzalez, and T. Nakajima. 2011. Ammonium perfluorooctanoate may cause testosterone reduction by adversely affecting testis in relation to PPARα. Toxicol. Lett. 205:265-272.
    a. ABSRACT: Perfluorooctanoate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, has the potential to lower testosterone levels as a result of testicular toxicity. To elucidate the mechanism and impact of PPARα on this reproductive toxicity, ammonium perfluorooctanoate (APFO) at doses of 0, 1.0 (low) mg/kg/day, or 5.0 (high) mg/kg/day was orally given daily to 129/sv wild-type (*mPPARα*), *Pparα*-null and PPARα-humanized (*hPPARα*) mice for 6 weeks. Both low- and high-dose APFO significantly reduced plasma testosterone concentrations in *mPPARα* and *hPPARα* mice, respectively. These decreases may, in part, be associated with decreased expression of mitochondrial cytochrome P450 side-chain cleavage enzyme, steroidogenic acute regulatory protein or peripheral benzodiazepine receptor as well as microsomal cytochrome $P450_{17\alpha}$ involved in the steroidogenesis. Additionally, both doses increased abnormalities in sperm morphology and vacuolated cells in the seminiferous tubules of both mouse lines. In contrast, APFO caused only a marginal effect either on the testosterone synthesis system or sperm and testis morphology in *Pparα*-null mice. These results suggest that APFO may disrupt testosterone biosynthesis by lowering the delivery of cholesterol into the mitochondria and decreasing the conversion of cholesterol to pregnenolone and androstandione in the testis of *mPPARα* and *hPPARα* mice, which may, in part, be related to APFO-induced mitochondrial damage.
    b. ANALYSIS: This mouse study used two doses of ammonium perfluorooctanoate (APFO), 1 and 5mg/kg/d administered orally to wild type, PPAR-alpha humanized and PPAR-alpha null mice for 6 weeks. The study looked at the effect of APFO on testosterone production. The data showed that both doses of APFO significantly reduced plasma testosterone levels, decreased expression of mitochondrial and microsomal cytochrome P450-related molecules associated with steroidogenesis. The treated animals also had abnormal sperm morphology and vacuolated cells in the seminiferous tubules. These effects were observed in the wild-type and humanized PPAR-alpha mice but were not that profound in the PPAR-alpha null mice.
    c. CONCLUSIONS: This study supports FDA's toxicology conclusion that "≥ C8 perfluorinated carboxylic acids appear to have direct adverse effects on reproductive hormone homeostasis" and "may therefore be considered as endocrine disruptors in male rats". This study provides further evidence of endocrine disruption in a different species, mouse, and at doses lower than previously assessed by FDA. Also, it adds a new finding: sperm and seminiferous tubules morphology is altered.

3. Macon, M.B., L.R. Villanueva, K. Tatum-gibbs, R.D. Zehr, M.J. Strynar, J.P. Stanko, S.S. White, L. Helfant, and S.E. Fenton. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low dose developmental effects and internal dosimetry. Toxicol.Sci. doi:10.1093/toxcie/kfr076

a. ABSTRACT: Perfluorooctanoic acid (PFOA) is an environmental contaminant that causes adverse developmental effects in laboratory animals. To investigate the low-dose effects of PFOA on offspring, timed-pregnant CD-1 mice were gavage dosed with PFOA for all or half of gestation. In the full-gestation study, mice were administered 0, 0.3, 1.0, and 3.0 mg PFOA/kg body weight (BW)/day from gestation days (GD) 1–17. In the late-gestation study, mice were administered 0, 0.01, 0.1, and 1.0 mg PFOA/kg BW/day from GD 10–17. Exposure to PFOA significantly ($p < 0.05$) increased offspring relative liver weights in all treatment groups in the full-gestation study and in the 1.0 mg PFOA/kg group in the late-gestation study. In both studies, the offspring of all PFOA-treated dams exhibited significantly stunted mammary epithelial growth as assessed by developmental scoring. At postnatal day 21, mammary glands from the 1.0 mg/kg GD 10–17 group had significantly less longitudinal epithelial growth and fewer terminal end buds compared with controls ($p < 0.05$). Evaluation of internal dosimetry in offspring revealed that PFOA concentrations remained elevated in liver and serum for up to 6 weeks and that brain concentrations were low and undetectable after 4 weeks. These data indicate that PFOA-induced effects on mammary tissue (1) occur at lower doses than effects on liver weight in CD-1 mice, an observation that may be strain specific, and (2) persist until 12 weeks of age following full-gestational exposure. Due to the low-dose sensitivity of mammary glands to PFOA in CD-1 mice, a no observable adverse effect level for mammary developmental delays was not identified in these studies.
b. ANALYSIS: In this study, gavaged pregnant mice were treated with one of three doses of PFOA (0.3, 1 and 3mg/kg/day) from GD1-17 or GD10-17. The offspring were studied for up to 12 weeks after birth. Regardless of the starting time of prenatal exposure, the offspring of all treated dams showed significant developmental delay in mammary gland development that persisted for three months after birth. Liver weight was increased in all offspring exposed during the full length of gestation regardless of the dose. PFOA serum and liver levels remained high measureable for up to six weeks after birth, while brain levels were lower and undetectable after 4 weeks.
c. CONCLUSION: This study supports FDA's analysis that the mammary gland is altered by PFOA; that the doses that cause mammary gland delay are lower than those inducing an increase in liver weight; adds information on PFOA accumulating in liver and found in offspring brains up to a month after birth. In sum, this study does not contradict FDA's toxicology conclusions regarding prenatal and postnatal endpoints.

4. Minata, M., K.H. Harada, A. Kärrman, T. Hitomi, M. Hirosawa, F.J. Gonzales, and A. Koizumi. 2010. Role of peroxisome proliferator-activated receptor-α in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver. Ind. Health 48: 96-107.
    a. ABSTRACT: Peroxisome proliferator-activated receptor-alpha (PPAR alpha) has been suggested to protect against chemically induced hepatobiliary injuries in rodents. This function could mask the potential toxicities of perfluorooctanoic acid (PFOA) that is an emerging environmental contaminant and a weak ligand of PPAR alpha. However its function has not been clarified. In this study, PFOA was found to elicit hepatocyte and bile duct injuries in Ppar alpha-null mice after 4 wk treatment with PFOA ammonium salt (0, 12.5, 25, 50 micromol/kg/d, gavage). In wild-type mice, PFOA caused major hepatocellular damage dose-dependently and minor

cholangiopathy observed only at 25 and 50 micromol/kg. In treated Ppar alpha-null mice, PFOA produced marked fat accumulation, severe cholangiopathy, hepatocellular damage and apoptotic cells especially in bile ducts. Oxidative stress was also increased 4-fold at 50 micromol/kg and TNF-alpha mRNA was upregulated more than 3-fold at 25 micromol/kg in Ppar alpha-null mice. Biliary bile acid/phospholipid ratios were higher in Ppar alpha-null mice than in wild-type mice. Results from these studies suggest that PPAR alpha is protective against PFOA and have a critical role in drug induced hepatobiliary injury.

b. ANALYSIS: This is a mouse study evaluating the role of PPAR alpha in liver toxicity. The study used wild-type and PPAR alpha null mice exposed to three doses of PFOA (12.5, 25 and 50 micromol/kg/d) by gavage. After four weeks of treatment the PPAR alpha null animals developed liver and bile duct injuries, fat accumulation and cholangiopathy. These animals also showed increased oxidative stress and altered bile chemistry.

c. CONCLUSION: These findings argue against the long-held theory that, in mice, liver toxicity is mediated by PPAR alpha mediated mechanism and therefore this endpoint is irrelevant to human health effects. In sum, this study does not contradict FDA's toxicology conclusions regarding any of the evaluated endpoints.

5. Onishchenko, N., C Fischer, W.N.W. Ibrahim, S. Negri, S. Spulbur, S. Cottica, and S. Ceccatelli. 2011. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. Neurotox. Res. 19:452-461. http://www.ncbi.nlm.nih.gov/pubmed/20512442

   a. ABSTRACT: Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are organic surfactants widely used in various industrial and consumer applications. Due to their chemical properties, these perfluorinated compounds (PFCs) have also become persistent contaminants. The risk of possible intrauterine and lactational exposure to these chemicals poses a significant health concern for potential developmental effects. In the present study we have found that dietary exposure of mice to 0.3 mg/kg of PFOS or PFOA throughout pregnancy results in different distribution pattern in the offspring brain and liver. In particular, exposure to PFOS led to four times higher accumulation of the chemical in the brains of newborn mice than PFOA. We have used a battery of behavioral tests to evaluate motor function, circadian activity, and emotion-related behavior in the exposed offspring. Exposure to PFOS resulted in decreased locomotion in a novel environment and reduced muscle strength only in male offspring. Prenatal exposure to PFOA was associated with changes in exploratory behavior in male and female offspring, as well as with increased global activity in males in their home cage. The neurobehavioral outcome of prenatal exposure to PFCs in mice is characterized by mild alterations in motor function and it appears to be sex-related.

   b. ANALYSIS: This is a mouse study with two groups, one control and one treated with PFOA at 0.3mg/kg/d in the diet; the dams were exposed through gestation and the offspring were tested at ages 5-8 weeks and 3-4 months old. Measurements included a battery of behavioral tests including motor function, circadian activity and emotion-related behavior. The findings include PFOA measurement in the newborns' brains and altered behavioral and motor activities in the offspring exposed in utero to PFOA.

c. CONCLUSION: These data supports FDA's toxicology report on prenatal and postnatal endpoints regarding "brief in utero exposure alone is sufficient to induce postnatal toxicity into adulthood."

6. Suh, C.H., N.K. Cho, C.K. Lee, C.H. Lee, D.W. Kim, J.H. Kim, B.C. Son, and J.T. Lee. 2011. Perfluorooctanoic acid-induced inhibition of placental-family hormone and fetal growth retardation in mice. Mol. Cell. Endocrinol. Doi:10.1016/j.mce.2011.01.009. http://www.ncbi.nlm.nih.gov/pubmed/21241770
    a. ABSTRACT: Perfluorooctanoic acid (PFOA) is a persistent pollutant worldwide and even found in human cord blood and breast milk. Some animal studies have reported that PFOA causes developmental toxicity such as fetal weight loss, but the mechanism is still unclear. This study focused on developmental toxicity of PFOA, particularly impacts of PFOA on placental endocrine function such as placental prolactin (PRL)-family hormone gene expression and fetal growth in mouse. Time-mated CD-1 mice were dosed by gavage with 0, 2, 10 and 25 mg/kg B.W/day of PFOA (n-10) dissolved with de-ionized water from gestational day (GD) 11-16. During treatment, body weight of each pregnant mouse was measured daily. On day 16, caesarean sections were performed and developmental data were observed. Three placentas from three different pregnant mice were assigned to each of the following experiments. The mRNA levels of mouse placental lactogen (mPL)-II, prolactin like protein (mPLP)-E, -F and Pit-1α and β isotype mRNAs, a transacting factor of mPLs and mPLPs genes, were analyzed using northern blot, in situ hybridization and RT-PCR, respectively. Maternal body weight gain was significantly declined from GD 13 in the PFOA treated groups compared to control. Developmental data such as fetal and placental weights were significantly decreased in accordance with PFOA dosage. Number of dead fetuses and post-implantation losses were significantly increased in the PFOA-exposed groups. In addition, placental efficiency (fetal weight/placental weight) was significantly reduced in PFOA treated groups in accordance with PFOA dosage. Histopathologic changes were observed in placenta. Dose dependent necrotic changes were observed in both 10 mg and 25 mg PFOA treated groups. Cell frequency of glycogen trophoblast cell and parietal trophoblast giant cell were decreased dose dependently in the junctional zone. In the labyrinth zone, sinusoidal trophoblast giant cell frequency was decreased in the 25 mg PFOA treated group. Also, morphological change such as crushed nuclear (atrophy) of trophoblast cells was observed in 25 mg PFOA treated group. Finally, mRNA levels of the mPL-II, mPLP-E, -F and Pit-1α and β were significantly reduced in the PFOA treated groups dose dependently. In addition, the changing pattern between mPL-II, mPLP-E, -F mRNA levels and fetal body weight showed positive relationship. In conclusion, the inhibitory effects of PFOA on the placental prolactin-family hormone genes expression may be secondary effects to insufficient trophoblast cell type differentiation and/or increased trophoblast cell necrosis. The impacts of PFOA on placental development and endocrine function reduced the placental efficiency and partly contributed to the fetal growth retardation in the mouse.
    b. ANALYSIS: This mouse study used three doses of PFOA (2, 10 and 25mg/kg/d) administered to dams from GD11-16 via gavage. The study looked at placental health and fetal development endpoints. The data showed that placental morphology

(including necrosis), cell differentiation and gene expression were altered in a dose-dependent manner. Placental and fetal weights were significantly reduced in all treated groups. The expression of genes related to the placental prolactin family was reduced likely due to the effect on placental development and functionality, which may have also delayed fetal growth.

c. CONCLUSION: These findings support FDA's toxicology conclusion that perfluoroalkyl compounds affect prenatal endpoints.

7. White, S.S., J.P. Stanko, K. Kato, A.M. Calafat, E.P. Hines, and S.E. Fenton. 2011. Gestional and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. Environ. Health Perspect. Doi:10.1289/ehp.1002741
    a. ABSTRACT: We treated P0 dams with 0, 1, or 5 mg PFOA/kg/day on gestation days 1-17. In addition, a second group of P0 dams treated with 0 or 1 mg/kg/day during gestation and their F1 and F2 offspring received continuous PFOA exposure (5 ppb) in drinking water. Resulting adult F1 females were bred to generate F2 offspring, whose development was monitored over postnatal days (PNDs) 1-63. F1 gland function was assessed on PND10 by timed-lactation experiments. Mammary tissue was isolated from P0, F1, and F2 females throughout the study and histologically assessed for age-appropriate development. PFOA-exposed F1 dams exhibited diminished lactational morphology, although F1 maternal behavior and F2 offspring body weights were not significantly affected by P0 treatment. In addition to reduced gland development in F1 females under all exposures, F2 females with chronic low-dose drinking-water exposures exhibited visibly slowed mammary gland differentiation from weaning onward. F2 females derived from 5 mg/kg PFOA-treated P0 dams displayed gland morphology similar to F2 chronic water exposure groups on PNDs 22-63. Gestational PFOA exposure induced delays in mammary gland development and/or lactational differentiation across three generations. Chronic, low-dose PFOA exposure in drinking water was also sufficient to alter mammary morphological development in mice, at concentrations approximating those found in contaminated human water supplies.
    b. ANALYSIS: This mouse study looked at effects of PFOA on the development of the mammary gland over two generations of females exposed at two different developmental times: 1) gestation only (from GD1-17) with doses of 1 and 5 mg/kg/d, and 2) gestation plus continuous postnatal exposure via drinking water at a 1mg/kg/d dose. The findings included: gestational exposure to PFOA delays mammary gland development and differentiation during lactation in parental, F1 and F2 generation of female mice. Chronic exposure to PFOA through drinking water also altered the mammary gland development across generations.
    c. CONCLUSION: This study supports FDA's toxicology conclusion that "brief in utero exposure alone is sufficient to induce postnatal toxicity into adulthood" and expands it to include long lasting effects through generations. In additions, it shows that continuous exposure to low doses starting *in utero* also have significant effects on the mammary gland.

8. Yahia, D., M.A. El-Nasser, M. Abedel-Latif, C. Tsukuba, M. Yoshida, I. Sato, and S. Tsuda. 2010. Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction. J. Toxicol. Sci. 35: 527-533.
    a. ABSTRACT: Perfluorooctanoic acid (PFOA) has similar characteristics to perfluorooctane sulfonate (PFOS) in reproduction toxicity featured by neonatal death. We found that PFOS exposure to mice during pregnancy led to intracranial blood vessel dilatation of fetuses accompanied by severe lung collapse which caused neonatal mortality. Thus, we adopted the corresponding experimental design to PFOS in order to characterize the neonatal death by PFOA. Pregnant ICR mice were given 1, 5 and 10 mg/kg PFOA daily by gavage from gestational day (GD) 0 to 17 and 18 for prenatal and postnatal evaluations, respectively. Five to nine dams per group were sacrificed on GD 18 for prenatal evaluation; other 10 dams were left to give birth. No maternal death was observed. The liver weight increased dose-dependently, with hepatocellular hypertrophy, necrosis, increased mitosis and mild calcification at 10 mg/kg. PFOA at 10 mg/kg increased serum enzyme activities (GGT, ALT, AST and ALP) with hypoproteinemia and hypolipidemia. PFOA treatment reduced the fetal body weight at 5 and 10 mg/kg. Teratological evaluation showed delayed ossification of the sternum and phalanges and delayed eruption of incisors at 10 mg/kg, but did not show intracranial blood vessel dilatation. Postnatal evaluation revealed that PFOA reduced the neonatal survival rate at 5 and 10 mg/kg. At 5 mg/kg pups were born alive and active and 16% died within 4 days observation, while all died within 6 hr after birth at 10 mg/kg without showing intracranial blood vessel dilatation. The cause of neonatal death by PFOA may be different from PFOS.
    b. ANALYSIS: This mouse study uses three doses of PFOA (1, 5 and 10mg/kg/d) administered to dams by gavage from GD 0-17 and 18. Prenatal and postnatal endpoints were evaluated. The findings included: fetal evaluation at GD17 showed reduced body weight, delayed ossification of the sternum and phalanges and delayed tooth eruption. At postnatal day 4 there was a 16% pup death in the middle dose group; all pups died hours after birth in the high dose group.
    c. CONCLUSION: This study supports FDA's toxicology assessment of similar prenatal and postnatal endpoints. In addition it also shows that the dam's liver and kidney weights increased in all doses, and brain weight was increased at the highest dose.

Rat Toxicology Studies

9. Butenhoff, J.L., G.L. Kennedy, Jr., S.-C. Chang, and G.W. Olsen. 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicol. 298:1-13. http://www.sciencedirect.com/science/article/pii/S0300483X12001151
    a. ABSTRACT: In order to assess the potential chronic toxicity and tumorigenicity of ammonium perfluorooctanoate (APFO), a 2-year dietary study was conducted with male and female rats fed 30 ppm or 300 ppm (approximately 1.5 and 15 mg/kg). In males fed 300 ppm, mean body weights were lower across most of the test period and survival in these rats was greater than that seen either in the 30 ppm or the control group. Non-neoplastic effects were observed in liver in rats fed 300 ppm and included elevated liver weight, an increase in the incidence of diffuse hepatocellular hypertrophy, portal mononuclear cell infiltration, and mild hepatocellular vacuolation without an increase in hepatocellular necrosis. Mean serum activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were elevated up to three times the control means, primarily at the 300 ppm dose. A significant increase in Leydig cell tumors of the testes was seen in the males fed 300 ppm, and tumors of the liver and acinar pancreas, which are often observed in rats from chronic exposure to peroxisome proliferating agents, were not observed in this study. All other tumor types were those seen spontaneously in rats of this stock and age and were not associated with feeding of APFO.
    b. ANALYSIS: This is a 2-year chronic and carcinogenesis study; rats were exposed to two doses of ammonium perfluorooctanoate (APFO) in the diet (1.5 and 15 mg/kg/day). The data showed a significant increase in testicular cancer in the high dose treatment. The liver also showed significant toxicity including increased weight, cell hypertrophy and vacualization and white blood cell infiltration; serum liver enzyme levels were also higher compared to untreated animals.
    c. CONCLUSION: This study supports FDA's toxicology evaluation regarding liver toxicity and carcinogenicity of perfluorocarboxylic compounds.

10. Cui, L., C. Liao, Q. Zhou, T. Xia, Z. Yun, and G. Jiang. 2010. Excretion of PFOA and PFOS in male rats during a subchronic exposure. Arch. Environ. Contam. Toxicol. 58: 205-213.
    a. ABSTRACT: Perfluorinated compounds (PFCs), a class of synthetic surfactants that are widely used, have become global environmental contaminants because of their high persistence and bioaccumulation. An increasing number of studies have described the pharmacokinetics of PFCs following in vivo exposure, however, few papers have focused on the excretion of these compounds during a period of consecutive exposure. In this study, the excretions of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) in male Sprague-Dawley rats gavaged consecutively for 28 days were investigated and compared. The faster elimination rate in urine compared to feces indicated that urinary excretion is the primary clearance route in rats for either PFOA or PFOS. During the first 24 h after administration of PFOA (5 and 20 mg/kg body weight/day), about 24.7-29.6% of the oral dose was excreted through urine and feces, while for PFOS, the excretion amounts were only 2.6-2.8% of the total gavaged doses (5 and 20 mg/kg body weight/day). The excretion

rates of both PFCs increased with increasing exposure doses. The higher elimination rate of PFOA through excretion indicated its lower accumulation in rats, thus inducing possible lower toxicities compared to PFOS.

b. ANALYSIS: This rat study used two doses of PFOA (5 and 20 mg/kg/d) administered to male rats for 28 consecutive days by gavage. It assessed the rate and route of excretion. The authors found that less than 30% of the oral dose was eliminated in feces and urine during the first 24 hours after administration of PFOA and the rate of elimination increased with time.
c. CONCLUSION: This study adds supporting data on excretion of PFOA and it does not contradict FDA's toxicology conclusions regarding any of the evaluated endpoints.

In summary, NRDC did not find anything in the 10 *in vivo* animal studies that contradicted FDA's conclusions, especially that perfluorocarboxylates should be treated as a class. On the contrary, we found additional evidence supporting FDA's conclusion that these chemicals cause adverse health effects in animals.

Recent publications on systematic reviews of PFOA exposure including human and animal data, and epidemiological study using biomonitoring NHANES data.

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth
Paula I. Johnson, Patrice Sutton, Dylan S. Atchley, Erica Koustas, Juleen Lam, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. Environ Health Perspect 122:1028–1039; http://dx.doi.org/10.1289/ehp.1307893

Background: The Navigation Guide methodology was developed to meet the need for a robust method of systematic and transparent research synthesis in environmental health science. We conducted a case study systematic review to support proof of concept of the method.
Objective: We applied the Navigation Guide systematic review methodology to determine whether developmental exposure to perfluorooctanoic acid (PFOA) affects fetal growth in humans.
Methods: We applied the first 3 steps of the Navigation Guide methodology to human epidemiological data: 1) specify the study question, 2) select the evidence, and 3) rate the quality and strength of the evidence. We developed a protocol, conducted a comprehensive search of the literature, and identified relevant studies using prespecified criteria. We evaluated each study for risk of bias and conducted meta-analyses on a subset of studies. We rated quality and strength of the entire body of human evidence.
Results: We identified 18 human studies that met our inclusion criteria, and 9 of these were combined through meta-analysis. Through meta-analysis, we estimated that a 1‑ng/mL increase in serum or plasma PFOA was associated with a –18.9 g (95% CI: –29.8, –7.9) difference in birth weight. We concluded that the risk of bias across studies was low, and we assigned a "moderate" quality rating to the overall body of human evidence.

Conclusion: On the basis of this first application of the Navigation Guide systematic review methodology, we concluded that there is "sufficient" human evidence that developmental exposure to PFOA reduces fetal growth.

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth.
Erica Koustas, Juleen Lam, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. Environ Health Perspect 122:1015–1027; http://dx.doi.org/10.1289/ehp.1307177

Background: In contrast to current methods of expert-based narrative review, the Navigation Guide is a systematic and transparent method for synthesizing environmental health research from multiple evidence streams. The Navigation Guide was developed to effectively and efficiently translate the available scientific evidence into timely prevention-oriented action.
Objectives: We applied the Navigation Guide systematic review method to answer the question "Does fetal developmental exposure to perfluorooctanoic acid (PFOA) or its salts affect fetal growth in animals ?" and to rate the strength of the experimental animal evidence.
Methods: We conducted a comprehensive search of the literature, applied prespecified criteria to the search results to identify relevant studies, extracted data from studies, obtained additional information from study authors, conducted meta-analyses, and rated the overall quality and strength of the evidence.
Results: Twenty-one studies met the inclusion criteria. From the meta-analysis of eight mouse gavage data sets, we estimated that exposure of pregnant mice to increasing concentrations of PFOA was associated with a change in mean pup birth weight of –0.023 g (95% CI: –0.029, –0.016) per 1-unit increase in dose (milligrams per kilogram body weight per day). The evidence, consisting of 15 mammalian and 6 nonmammalian studies, was rated as "moderate" and "low" quality, respectively.
Conclusion: Based on this first application of the Navigation Guide methodology, we found sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth
Juleen Lam, Erica Koustas, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. Environ Health Perspect 122:1040–1051; http://dx.doi.org/10.1289/ehp.1307923

Background: The Navigation Guide is a novel systematic review method to synthesize scientific evidence and reach strength of evidence conclusions for environmental health decision making.
Objective: Our aim was to integrate scientific findings from human and nonhuman studies to determine the overall strength of evidence for the question "Does developmental exposure to

perfluorooctanoic acid (PFOA) affect fetal growth in humans?"
Methods: We developed and applied prespecified criteria to systematically and transparently a) rate the quality of the scientific evidence as "high," "moderate," or "low"; b) rate the strength of the human and nonhuman evidence separately as "sufficient," "limited," "moderate," or evidence of lack of toxicity"; and c) integrate the strength of the human and nonhuman evidence ratings into a strength of the evidence conclusion.
Results: We identified 18 epidemiology studies and 21 animal toxicology studies relevant to our study question. We rated both the human and nonhuman mammalian evidence as "moderate" quality and "sufficient" strength. Integration of these evidence ratings produced a final strength of evidence rating in which review authors concluded that PFOA is "known to be toxic" to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.
Conclusion: We concluded that developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species. The results of this case study demonstrate the application of a systematic and transparent methodology, via the Navigation Guide, for reaching strength of evidence conclusions in environmental health.

Perfluoroalkyl Chemicals and Asthma among Children 12–19 Years of Age: NHANES (1999–2008)
Olivier Humblet, Ledif Grisell Diaz-Ramirez, John R. Balmes, Susan M. Pinney, and Robert A. Hiatt. Environ Health Perspect 122:1129–1133; http://dx.doi.org/10.1289/ehp.1306606

Background: Perfluoroalkyl chemicals (PFCs) are a family of commonly used industrial chemicals whose persistence and ubiquity in human blood samples has led to concern about possible toxicity. Several animal studies and one recent human study have suggested a link between exposure to PFCs and asthma, although few epidemiologic studies have been conducted.
Objectives: We investigated children's PFC serum concentrations and their associations with asthma-related outcomes.
Methods: We evaluated the association between serum concentrations of eight PFCs, including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS), with self-reported lifetime asthma, recent wheezing, and current asthma using data from participants 12–19 years of age from the 1999–2000 and 2003–2008 National Health and Nutrition Examination Surveys.
Results: In multivariable-adjusted models, PFOA was associated with higher odds of ever having received a diagnosis of asthma [odds ratio (OR) = 1.18; 95% CI: 1.01, 1.39 for a doubling in PFOA], whereas for PFOS there were inverse relationships with both asthma and wheezing (OR = 0.88; 95% CI: 0.74, 1.04, and OR = 0.83; 95% CI: 0.67, 1.02, respectively). The associations were attenuated after accounting for sampling weights. No associations were seen between the other PFCs and any outcome.

Conclusions: This cross-sectional study provides some evidence for associations between exposure to PFCs and asthma-related outcomes in children. The evidence is inconsistent, however, and prospective studies are needed.

Appendix 6
Long-Chain Perfluorocarboxylates Removed from Commerce in 2011.

Table A-1: Effective Food Contact Substance Notifications for Long-Chain Perfluorocarboxylates for which the manufacturer voluntarily ceased introduction into interstate commerce in 2011 in response to FDA's 2010 request.

FCN No.	Manufacturer	Description of Food Contact Substance (FCS) covered by the effective FCS Notification (FCN)	Intended Use	Effective Date (before cessation)
59	BASF Corp.	Glycine, N,N-bis[2-hydroxy-3-(2-propenyloxy)propyl]-, monosodium salt, reaction products with ammonium hydroxide and pentafluoroiodoethane-tetrafluoroethylene telomer (CAS Reg. No. 220459-70-1).	As a component of paper and paperboard in contact with nonalcoholic food.	August 16, 2000
206	DuPont Chemical Solutions Enterprise	Copolymer of 2-perfluoroalkylethyl acrylate, 2-N,N-diethylaminoethyl methacrylate, and glycidyl methacrylate.	As an oil and grease-resistant treatment for paper and paperboard intended for food-contact use.	June 12, 2002
255	BASF Corp.	3-cyclohexane-1-carboxylic acid, 6-((di-2-propenylamino)carbonyl)-,(1R,6R), reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, ammonium salts.	As an oil repellent sizing agent in the production of paper and paperboard.	September 5, 2002
311	DuPont Chemical Solutions Enterprise	Copolymers of 2-perfluoroalkylethyl acrylate, 2-N,N-diethylaminoethyl methacrylate, and glycidyl methacrylate.	As an oil or grease resistant treatment for paper and paperboard intended for single service use in microwave heat-susceptor packaging; the food-contact substance is intended to contact all food types.	April 15, 2003
338	DuPont Chemical Solutions Enterprise	Copolymers of 2-perfluoroalkylethyl acrylate, 2-N,N-diethylaminoethyl methacrylate, and glycidyl methacrylate.	As an oil or grease resistant treatment for paper and paperboard intended for food-contact use.	August 19, 2003

628	Clariant Corp.	Copolymer of 2-perfluoroalkylethyl acrylate, 2-(dimethylamino)ethyl methacrylate, and oxidized 2-(dimethylamino)ethyl methacrylate (CAS Reg. No. 479029-28-2).	As an oil and grease repellent in the manufacture of paper and paperboard.	October 10, 2006
646	DuPont Chemical Solutions Enterprise	Copolymers of 2-perfluoroalkylethyl acrylate, 2-N,N-diethylaminoethyl methacrylate, glycidyl methacrylate, acrylic acid, and methacrylic acid (CAS Reg. No. 870465-08-0).	As an oil and grease resistant treatment for paper and paperboard employed either prior to the sheet forming operation or at the size press.	September 30, 2006
See http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/Notifications/ucm308462.htm.				

Appendix 7
Requested Changes to 21 C.F.R. § 176.170

[Code of Federal Regulations]
[Title 21, Volume 3]
[Revised as of April 1, 2013]
[CITE: 21CFR176.170]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)
PART 176 -- INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS
Subpart B--Substances for Use Only as Components of Paper and Paperboard

Sec. 176.170 Components of paper and paperboard in contact with aqueous and fatty foods.

Substances identified in this section may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods, subject to the provisions of this section. Components of paper and paperboard in contact with dry food of the type identified under Type VIII of table 1 in paragraph (c) of this section are subject to the provisions of 176.180.
(a) Substances identified in paragraph (a) (1) through (5) of this section may be used as components of the food-contact surface of paper and paperboard. Paper and paperboard products shall be exempted from compliance with the extractives limitations prescribed in paragraph (c) of this section:*Provided,* That the components of the food-contact surface consist entirely of one or more of the substances identified in this paragraph:*And provided further,* That if the paper or paperboard when extracted under the conditions prescribed in paragraph (c) of this section exceeds the limitations on extractives contained in paragraph (c) of this section, information shall be available from manufacturing records from which it is possible to determine that only substances identified in this paragraph (a) are present in the food-contact surface of such paper or paperboard.
(1) Substances generally recognized as safe in food.
(2) Substances generally recognized as safe for their intended use in paper and paperboard products used in food packaging.
(3) Substances used in accordance with a prior sanction or approval.
(4) Substances that by regulation in parts 170 through 189 of this chapter may be safely used without extractives limitations as components of the uncoated or coated food-contact surface of paper and paperboard in contact with aqueous or fatty food, subject to the provisions of such regulation.
(5) Substances identified in this paragraph, as follows:

List of Substances	**Limitations**
Acetyl peroxide	For use only as polymerization catalyst.
Acrylamide-methacrylic acid-maleic anhydride copolymers containing not more than 0.2 percent of	For use only as a retention aid employed prior to t

residual acrylamide monomer and having an average nitrogen content of 14.9 percent such that a 1 percent by weight aqueous solution has a minimum viscosity of 600 centipoises at 75 deg. F, as determined by LVG-series Brookfield viscometer (or equivalent) using a No. 2 spindle at 30 r.p.m	sheet-forming operation in the manufacture of paper and paperboard in such an amount that the finished paper and paperboard will contain the additive at a level not in excess of 0.05 percent by weight of dry fibers in the finished paper and paperboard.
Acrylamide-[beta]-methacrylyloxyethyltrimethylammonium methyl sulfate copolymer resins containing not more than 10 molar percent of [beta]-methacrylyloxyethyltrimethylammonium methyl sulfate and containing less than 0.2% of residual acrylamide monomer	For use only as a retention aid and flocculant employed prior to the sheet-forming operation in the manufacture of paper and paperboard.
Acrylic acid, sodium salt copolymer with polyethyleneglycol allyl ether (CAS Reg. No. 86830-15-1)	For use only in paper mill boilers.
Acrylic acid copolymer with 2-acrylamido-2-methylpropane-sulfonic acid (CAS Reg. No. 40623-75-4) and/or its ammonium/alkali metal mixed salts. The copolymer is produced by poly-merization of acrylic acid and 2-acrylamido-2-methylpropane-sulfonic acid in a weight ratio of 60/40, such that a 28 percent by weight aqueous solution of the polymer has a viscosity of 75-150 centipoises at 25 deg. C as determined by LV-series Brookfield viscometer (or equivalent) using a No. 2 spindle at 60 r.p.m	For use only as a scale inhibitor prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 1.0 kilogram (2.2 pounds) of copolymer per 907 kilograms (1 ton) of dry paper and paperboard fibers.
Acrylonitrile polymer, reaction product with ethylenediamine sulfate having a nitrogen content of 22.5-25.0 percent (Kjeldahl dry basis) and containing no more than 0.075 percent monomer as ethylenediamine. The finished resin in a 24 percent by weight aqueous solution has a viscosity of 1,000-2,000 centipoises at 25 deg. C as determined by LVT-series Brookfield viscometer using a No. 4 spindle at 50 r.p.m. (or by other equivalent method)	For use only as a size promoter and retention aid at a level not to exceed 0.5 percent by weight of the dry paper and paperboard.
Acrylonitrile polymer with styrene, reaction product with ethylenediamine acetate, having a nitrogen content of 7.4-8.3 percent (Kjeldahl dry basis) and containing no more than 0.25 percent monomer as ethylenediamine	1. For use only as a sizing material applied after the sheet-forming operation in the manufacture of paper and paperboard in such amount that the paper and paperboard will contain the additive at a level not in excess of 0.25 percent by weight of the dry paper and paperboard.2. For use only as a sizing material applied prior to the sheet-forming operation in the manufacture of paper and paperboard in such amount that the paper and paperboard will contain the additive at a level not in excess of 1.0 percent by weight of the dry paper and paperboard.
1-Alkenyl olefins, containing not less than 72 percent of $C_{30}$and higher olefins	For use only under the following conditions:1. In coatings for paper and paperboard with food of Types I, II, IV-B, and VII-B described in table 1 of paragraph (c) of this section under conditions of use E, F, and G described in table 2 of paragraph (c) of this section.2. In coatings for paper and paperboard

	with food of Type VIII described in table I of paragraph (c) of this section under conditions of use A through H described in table 2 of paragraph (c) of this section.
(2-Alkenyl) succinic anhydrides mixture, in which the alkenyl groups are derived from olefins which contain not less than 95 percent of C_{15}-C_{21}groups	For use only as a sizing agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 1 percent by weight of the finished dry paper and paperboard fibers.
Alkyl(C_{12}-C_{20})methacrylatemethacrylic acid copolymers (CAS Reg. No. 27401-06-5)	For use only as stabilizers employed prior to the sheet-forming operation in the manufacture of paper and paperboard.
tert-Alkyl(C_8-C_{16})mercaptans	For use only as polymerization-control agent.
Aluminum acetate	
2-Amino-2-methyl-1-propanol (CAS Reg. No. 124-68-5)	For use as a dispersant for pigment suspension at a level not to exceed 0.25 percent by weight of pigment. The suspension is used as a component of coatings for paper and paperboard under conditions of use described in paragraph (c) of this section, table 2, conditions of use E through G.
Ammonium bis(*N*-ethyl-2-perfluoroalkylsulfonamido ethyl) phosphates, containing not more than 15% ammonium mono (*N*-ethyl-2-perfluoroalkylsulfonamido ethyl) phosphates, where the alkyl group is more than 95% $C_8$and the salts have a fluorine content of 50.2% to 52.8% as determined on a solids basis	For use only as an oil and water repellant at a level not to exceed 0.17 pound (0.09 pound of fluorine) per 1,000 square feet of treated paper or paperboard of a sheet basis weight of 100 pounds or less per 3,000 square feet of paper or paperboard, and at a level not to exceed 0.5 pound (0.26 pound of fluorine) per 1,000 square feet of treated paper or paperboard having a sheet basis weight greater than 100 lb. per 3,000 square feet as determined by analysis for total fluorine in the treated paper or paperboard without correction for any fluorine that might be present in the untreated paper or paperboard, when such paper or paperboard is used as follows:1. In contact, under conditions of use C, D, E, F, G, or H described in table 2 of paragraph (c) of this section, with nonalcoholic food.2. In contact with bakery products

	of Type VII, VIII, and IX described in table I of paragraph (c) of this section under good manufacturing practices of commercial and institutional baking.
Ammonium persulfate	
Ammonium thiosulfate	
Ammonium zirconium carbonate (CAS Reg. No. 32535-84-5) and its tartaric acid adduct	For use only as an insolubilizer for binders used in coatings for paper and paperboard, and limited to use at a level not to exceed 2.5 percent by weight of coating solids.
Ammonium zirconium citrate (CAS Reg. No. 149564-62-5), ammonium zirconium lactate-citrate (CAS Reg. No. 149564-64-7), ammonium zirconium lactate (CAS Reg. No. 149564-63-6)	For use as insolubilizers with protein binders in coatings for paper and paperboard, at a level not to exceed 1.4 percent by weight of coating solids.
Anionic polyurethane, produced by reacting the preliminary adduct formed from the reaction of glyceryl monostearate and 2,4-toluenediisocyanate with not more than 10 mole percent*N*-methyldiethanolamine and not less than 90 mole percent dimethylolpropionic acid. The final product is a 15 to 20 percent by weight aqueous solution, having a Brookfield viscosity of 25 to 100 centipoises at 24 deg. C (75 deg. F)	For use only as a surface sizing agent at a level not to exceed 0.1 percent by weight of dry paper and paperboard.
9,10-Anthraquinone (Chemical Abstracts Service Registry No. 84-65-1) which has a purity of not less than 98 percent	For use only as a pulping aid in the alkaline pulping of lignocellulosic material at levels not to exceed 0.1 percent by weight of the raw lignocellulosic material.
Aromatic petroleum hydrocarbon resin, hydrogenated (CAS Reg. No. 88526-47-0), produced by the catalytic polymerization of aromatic substituted olefins from low boiling distillates of cracked petroleum stocks with a boiling point no greater than 220 deg. C (428 deg. F), and the subsequent catalytic reduction of the resulting aromatic petroleum hydrocarbon resin. The resin meets the following specifications: softening point 85 deg. C (185 deg. F) minimum, as determined by ASTM Method E 28-67 (Reapproved 1982), "Standard Test Method for Softening Point by Ring-and-Ball Apparatus," and aniline point 70 deg. C (158 deg. F) minimum, as determined by ASTM Method D 611-82, "Standard Test Methods for Aniline Point and Mixed Aniline Point of Petroleum Products and Hydrocarbon Solvents," which are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from the American Society for Testing and Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*	For use only as modifiers in wax polymer blend coatings for paper and paperboard at a level not to exceed 50 weight-percent of the coating solids under conditions of use E, F, and G identified in table 2 of paragraph (c) of this section.
Azo-bisisobutyronitrile	For use only as polymerization catalyst.

1,2-Benzisothiazolin-3-one (CAS Registry No. 2634-33-5)	For use only as a preservative in paper coating compositions and limited to use at a level not to exceed 0.01 mg/in^2(0.0016 mg/cm^2) of the finished paper and paperboard.
Benzoyl peroxide	Do.
N,*N*-Bis(2-hydroxyethyl)alkyl (C_{12}-C_{18})amide	For use only as an adjuvant to control pulp absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet forming operation.
Bis(methoxymethyl)tetrakis-[(octadecyloxy)-methyl]melamine resins having a 5.8-6.5 percent nitrogen content (CAS Reg. No. 68412-27-1)	For use only under the following conditions:1. As a water repellant employed prior to the sheet-forming operation in the manufacture of paper and paperboard in such amount that the finished paper and paperboard will contain the additive at a level not in excess of 1.6 percent by weight of the finished dry paper and paperboard fibers.2. The finished paper and paperboard will be used in contact with nonalcoholic foods only.3. As a water repellant employed after the sheet-forming operation in the manufacture of paper and paperboard in such amount that the finished paper and paperboard will contain the additive at a level not to exceed 1.6 percent by weight of the finished dry paper and paperboard fibers. The finished paper and paperboard will be used only in contact with food of Types I, II, IV-B, VI, VII-B, and VIII described in table 1 of paragraph (c) of this section.
2-Bromo-2-nitro-1,3-propanediol (CAS Reg. No. 52-51-7)	For use only as an antimicrobial/preservative in fillers, pigment slurries, starch sizing solutions, and latex coatings at levels not to exceed 0.01 percent by weight of those components.
Butanedioic acid, sulfo-1,4-di-(C_9-C_{11}alkyl) ester, ammonium salt (also known as butanedioic acid, sulfo-1,4-diisodecyl ester, ammonium salt [CAS Reg. No. 144093-88-9]).	For use as a surface active agent in package coating inks at levels not to exceed 3 percent by weight of the coating ink.
tert-Butyl hydroperoxide	For use only as polymerization catalyst.
tert-Butyl peroxide	Do.

Calcium isostearate	For use only with*n*-decyl alcohol as a stabilizing material for aqueous calcium stearate dispersions intended for use as components of coatings for paper and paperboard.
Carrageenan and salts of carrageenan as described in 172.620 and 172.626 of this chapter	
Castor oil, hydrogenated	
Castor oil, sulfated, ammonium, potassium, or sodium salt	
Cellulose, regenerated	
Chloracetamide	For use only as polymerization-control agent.
Cobaltous acetate	For use only as polymerization catalyst.
Cumene hydroperoxide	Do.
Cyanoguanidine	For use only:1. As a modifier for amino resins.2. As a fluidizing agent in starch and protein coatings for paper and paperboard.
n-Decyl alcohol	For use only with calcium isostearate as a stabilizing material for aqueous calcium stearate dispersions intended for use as components of coatings for paper and paperboard.
Dialdehyde guar gum	For use only as a wet-strength agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 1% by weight of the finished dry paper and paperboard fibers.
Dialdehyde locust bean gum	Do.
Dialkyl(C_{16}-C_{18})carbamoyl chloride (CAS Reg. No. 41319-54-4) manufactured by the reaction of secondary amines derived from fatty acids of animal or vegetable sources with phosgene	For use as a sizing agent at a level not to exceed 0.2 percent by weight of the dry fiber.

Diallyldimethyl ammonium chloride polymer with acrylamide and potassium acrylate, produced by copolymerizing either (1) diallyldimethyl ammonium chloride and acrylamide in a weight ratio of 50/50, with 4.4 percent of the acrylamide subsequently hydrolyzed to potassium acrylate or (2) polymerized diallyldimethyl ammonium chloride, acrylamide and potassium acrylate (as acrylic acid) in a weight ratio of 50/47.8/2.2, respectively, so that the finished resin in a 1 percent by weight aqueous solution (active polymer) has a viscosity of more than 22 centipoises at 22 deg. C (72 deg. F) as determined by LVF series, Brookfield Viscometer using No. 1 spindle at 60 RPM (or by other equivalent method) (CAS Reg. No. 25136-75-8)	For use only as a retention and/or drainage aid employed prior to the sheet-forming operations in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.05 percent by weight of the finished paper and paperboard.
Diallyldimethylammonium chloride with acrylamide (CAS Reg. No. 26590-05-6). The copolymer is produced by copolymerizing diallyldimethylammonium chloride with acrylamide in a weight ratio of 50-50 so that the finished resin in a 1 percent by weight aqueous solution (active polymer) has a viscosity of more than 22 centipoises at 22 deg. C (71.6 deg. F), as determined by LVF-series Brookfield viscometer using a No. 1 spindle at 60 r.p.m. (or by other equivalent method)	For use only as a drainage and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.05 percent by weight of the finished paper and paperboard.
Diallyldiethylammonium chloride polymer with acrylamide, and diallyldimethylammonium chloride, produced by copolymerizing acrylamide, diallyldiethylammonium chloride, and diallyldimethylammonium chloride, respectively, in the following weight ratios and having viscosities determined at 22 deg. C, by LVF-series Brookfield viscometer using a No. 1 spindle at 60 r.p.m. (or by other equivalent method), as follows:	
1. Weight ratio: 50-2.5-47.5. The finished resin in a 1 percent by weight aqueous solution has a minimum viscosity of 22 centipoises	For use only as a retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.05 percent by weight of the finished paper and paperboard.
2. Weight ratio: 25-2.5-72.5. The finished resin in a 0.20 percent by weight aqueous solution has a minimum viscosity of 20 centipoises	For use only as a drainage and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.075 percent by weight of the finished paper and paperboard.
3. Weight ratio: 80-2.5-17.5. The finished resin in a 0.30 percent by weight aqueous solution has a minimum viscosity of 50 centipoises	For use only as a drainage and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.075 percent by weight of the finished paper and paperboard.
Diallyldiethylammonium chloride polymer with acrylamide, potassium acrylate, and diallyldimethylammonium chloride. The polymer is produced by copolymerizing either: (1) acrylamide, diallyldiethylammonium chloride, and diallyldimethylammonium chloride in a weight ratio of 50-2.5-	For use only as a retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to

47.5, respectively, with 4.4 percent of the acrylamide subsequently hydrolyzed to potassium acrylate, or (2) acrylamide, potassium acrylate (as acrylic acid), diallyldiethylammonium chloride, and diallyldimethylammonium chloride in a weight ratio of 47.8-2.2-2.5-47.5, so that the finished resin in a 1 percent by weight aqueous solution has a minimum viscosity of 22 centipoises at 22 deg. C, as determined by LVF-series Brookfield viscometer using a No. 1 spindle at 60 r.p.m. (or by other equivalent method)	exceed 0.05 percent by weight of the finished paper and paperboard.
Diallyldimethylammonium chloride polymer with acrylamide, reaction product with glyoxal, produced by copolymerizing not less than 90 weight percent of acrylamide and not more than 10 weight percent of diallyldimethylammonium chloride, which is then cross-linked with not more than 30 weight percent of glyoxal, such that a 10 percent aqueous solution has a minimum viscosity of 25 centipoises at 25 deg. C as determined by Brookfield viscometer Model RVF, using a No. 1 spindle at 100 r.p.m	For use only as a dry and wet strength agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard in such an amount that the finished paper and paperboard will contain the additive at a level not in excess of 2 percent by weight of the dry fibers in the finished paper and paperboard.
2,2-Dibromo-3-nitrilopropionamide (CAS Reg. No.10222-01-2).	For use as a preservative at a level not to exceed 100 parts per million in coating formulations and in component slurries and emulsions, used in the production of paper and paperboard and coatings for paper and paperboard.
2,5-Di-*tert*-butyl hydroquinone	For use only as an antioxidant for fatty based coating adjuvants provided it is used at a level not to exceed 0.005% by weight of coating solids.
Diethanolamine	For use only:1. As an adjuvant to control pulp absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet-forming operation.2.In paper mill boilers.
~~Diethanolamine salts of mono- and bis (1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C_8-$C_{18}$and the salts have a fluorine content of 52.4% to 54.4% as determined on a solids basis~~	~~For use only as an oil and water repellant at a level not to exceed 0.17 pound (0.09 pound of fluorine) per 1,000 square feet of treated paper or paperboard, as determined by analysis for total fluorine in the treated paper or paperboard without correction for any fluorine which might be present in the untreated paper or paperboard, when such paper or paperboard is used in contact with nonalcoholic foods under the conditions of use described in paragraph (c) of this section, table 2, conditions of use (B) through (H).~~
Diethyl(2-hydroxyethyl) methylammonium methyl sulfate, acrylate, polymer with acrylamide, chemical	For use only as a retention aid and drainage aid

abstract service registry No. [26796-75-8] having 90-95 mole pct. acrylamide, a nitrogen content of not more than 19.7 pct. (Kjeldahl, dry basis), and a residual acrylamide monomer content of not more than 0.1 pct. The finished polymer in a 1 pct. by weight aqueous solution has a minimum viscosity of 900 centipoises at 25 deg. C as determined by LVT-series Brookfield viscometer using a No. 2 spindle at 12 r.p.m. (or by equivalent method)	employed prior to the sheet-forming operation in the manufacture of paper and paperboard at a level not to exceed 0.15 pct. by weight of finished dry paper and paperboard fibers.
Diethylenetriamine	For use only as a modifier for amino resins.
N,*N*-Diisopropanolamide of tallow fatty acids	For use only as an adjuvant to control pulp absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet-forming operation.
Dimethylamine-epichlorohydrin copolymer in which not more than 5 mole-percent of dimethylamine may be replaced by an equimolar amount of ethylenediamine and in which the ratio of total amine to epichlorohydrin does not exceed 1:1. The nitrogen content of the copolymer shall be 9.4 to 10.8 weight percent on a dry basis and a 10 percent by weight aqueous solution of the final product has a minimum viscosity of 5.0 centipoises at 25 deg. C, as determined by LVT-series Brookfield viscometer using a No. 1 spindle at 60 r.p.m. (or by other equivalent method)	For use only:1. As a retention aid employed before the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 1 percent by weight of the finished paper and paperboard.2. At the size press at a level not to exceed 0.017 percent by weight of the finished paper and paperboard.
N-[(Dimethylamino)methyl]-acrylamide polymer with acrylamide and styrene having a nitrogen content of not more than 16.9 percent and a residual acrylamide monomer content of not more than 0.2 percent on a dry basis	For use only as a dry-strength agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 1 percent by weight of finished dry paper or paperboard fibers.
N,*N'*-Dioleoylethylenediamine	
Diphenylamine	For use only as an antioxidant for fatty based coating adjuvants provided it is used at a level not to exceed 0.005% by weight of coating solids.
Dipropylene glycol	
Disodium salt of 1,4-dihydro-9,10-dihydroxyanthracene (CAS Reg. No. 73347-80-5)	For use only as a catalyst in the alkaline pulping of lignocellulosic materials at levels not to exceed 0.1 percent by weight of the raw lignocellulosic materials.
N,*N'*-Distearoylethylenediamine	
n-Dodecylguanidine acetate	For use only as an antimicrobial agent in paper and paperboard under the following conditions:
1. For contact only with nonalcoholic food having a pH above 5 and provided it is used at a level not to	

exceed 0.4 percent by weight of the paper and paperboard.2. For use in the outer ply of multiwall paper bags for contact with dry food of Type VIII described in table I of paragraph (c) of this section and provided it is used at a level of 0.8 percent by weight of the paper.	
n-Dodecylguanidine hydrochloride	For use only as an antimicrobial agent in paper and paperboard under the following conditions:1. For contact only with nonalcoholic food having a pH above 5 and provided it is used at a level not to exceed 0.4 percent by weight of the paper and paperboard.2. For use in the outer ply of multiwall paper bags for contact with dry food of Type VIII described in table I of paragraph (c) of this section and provided it is used at a level of 0.8 percent by weight of the paper.
Fatty acids derived from animal and vegetable fats and oils and salts of such acids, single or mixed, as follows:	
Aluminum.	
Ammonium.	
Calcium.	
Magnesium.	
Potassium.	
Sodium.	
Zinc.	
Ferric chloride	
Ferrous ammonium sulfate	
Fish oil, hydrogenated	
Fish oil, hydrogenated, potassium salt	
Furcelleran and salts of furcelleran as described in 172.655 and 172.660 of this chapter	
Glutaraldehyde (CAS Reg. No. 111-30-8)	For use only as an antimicrobial agent in pigment and filler slurries used in the manufacture of paper and paperboard at levels not to exceed 300 parts per million by weight of the slurry solids.
Glyceryl lactostearate	

Glyceryl mono-1,2-hydroxystearate	
Glyceryl monoricinoleate	
Guar gum modified by treatment with [beta]-diethylamino- ethyl chloride hydrochloride	For use only as a retention aid and/or drainage aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard.
Guar gum modified by treatment with not more than 25 weight percent of 2,3-epoxypropyltri-methylammonium chloride such that the finished product has a maximum chlorine content of 4.5 percent, a maximum nitrogen content of 3.0 percent, and a minimum viscosity in 1-percent-by-weight aqueous solution of 1,000 centipoises at 77 deg. F, as determined by RV-series Brookfield viscometer (or equivalent) using a No. 3 spindle at 20 r.p.m	For use only as a retention aid and/or internal size employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and limited to use at a level: (1) Not to exceed 0.15 percent by weight of the finished dry paper and paperboard fibers intended for use in contact with all types of foods, except (2) not to exceed 0.30 pct. by weight of the finished dried paper and paperboard fibers for use with nonalcoholic and nonfatty food of types identified under Types I, II, IV-B, VI-B, VII-B, and VIII of table I in par. (c) of this section.
N,N,N',N',N[Prime],N[Prime]-Hexakis (methoxymethyl)-1,3,5-triazine-2,4,6-triamine polymer with stearyl alcohol, [alpha]-octadecenyl-omega-hydroxypoly(oxy-1,2-ethanediyl), and alkyl (C20+) alcohols (CAS Reg. No. 130328-24-4)	For use only as a water-repellent applied to the surface of paper and paperboard at levels not to exceed 1 percent by weight of the finished dry paperboard fibers. The finished paper and paperboard will be used in contact with aqueous foods under conditions of use B through G as described in table 2 of paragraph (c) of this section.
Hexamethylenetetramine	For use only as polymerization cross-linking agent for protein, including casein.
Hydroquinone and the monomethyl or monoethyl ethers of hydroquinone	For use only as an inhibitor for monomers.
Hydroxymethyl-5,5-dimethylhydantoin (CAS Reg. No. 27636-82-4), mixture with 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin (CAS Reg. No. 6440-58-0)	For use only as a preservative in clay-type fillers at a level not to exceed a combined total of 1,200 milligrams/kilograms hydroxymethyl-5,5-dimethylhydantoin and 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin in the filler.
Hydroxypropyl guar gum having a minimum viscosity of 5,000 centipoises at 25 deg. C., as determined by RV-series Brookfield viscometer using a No. 4 spindle at 20 r.p.m. (or other suitable method) and using a test sample prepared by dissolving 5 grams of moisture-free hydroxypropyl guar gum in 495 milliliters of a 70 percent by weight aqueous propylene glycol solution	For use only as a dry strength and formation aid agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 1.5 percent by weight of finished

	dry paper or paperboard fibers.
12-Hydroxystearic acid-polyethylene glycol block copolymers (CAS Reg. No. 70142-34-6) produced by the reaction of polyethylene glycol (minimum molecular weight 200) with 12-hydroxystearic acid	For use only as a surfactant for dispersions of polyacrylamide retention and drainage aids employed prior to the sheet forming operation in the manufacture of paper and paperboard.
Imidazolium compounds, 2-($C_{17}$and C_{17}-unsaturated alkyl)-1-[2-($C_{18}$and C_{18}-unsaturated amido)ethyl]-4,5-dihydro-1-methyl, methyl sulfates (CAS Reg. No. 72749-55-4).	For use only at a level not to exceed 0.5 percent by weight of the dry paper and paperboard.
Isopropyl*m*-and*p*-cresols (thymol derived)	For use only as an antioxidant for fatty based coating adjuvants provided it is used as a level not to exceed 0.005% by weight of coating solids.
Isopropyl peroxydicarbonate	For use only as polymerization catalyst.
Japan wax	
Lanolin	
Lauryl peroxide	For use only as polymerization catalyst.
Lauryl sulfate salts:	
Ammonium.	
Magnesium.	
Potassium.	
Sodium.	
Lecithin, hydroxylated	
Lignin sulfonate and its calcium, potassium, and sodium salts	
Maleic anhydride, polymer with ethyl acrylate and vinyl acetate, hydrolyzed (CAS Reg. No. 113221-69-5) and/or its ammonium, potassium, and sodium salts	For use only as a deposit control additive prior to the sheet forming operation to prevent scale buildup in the manufacture of paper and paperboard in contact with food, at a level not to exceed 0.075 percent (as the acid) by weight of the dry paper and paperboard.
Methacrylic acid-acrylic acid copolymer (CAS Reg. No. 25751-21-7)	For use only as a boiler water additive at a level not to exceed 50 parts per million in the boiler water.
N-methyldiallylamine hydrochloride polymer with epichlorohydrin having a nitrogen content of 4.8 to 5.9 percent (Kjeldahl dry basis) such that a 20 percent by weight aqueous solution has a minimum viscosity of 30 centipoises and maximum viscosity of 100 centipoises at 25 deg. C, as determined by LVF Model Brookfield viscometer using a No. 1 spindle at 60 r.p.m. (or equivalent method)	For use only as a retention aid, flocculating agent, and wet-strength agent employed in the manufacture of paper and paperboard prior to the sheet-forming operation and limited to use at a level not to exceed

	1.5 percent by weight of the dry paper and paperboard.
Methyl naphthalene sulfonic acid-formaldehyde condensate, sodium salt	For use only as an adjuvant to control pulp absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet-forming operation.
N-methyl-*N*-(tall oil acyl) taurine, sodium salt (CAS Reg. No. 61791-41-1)	For use only to control scale formation in the manufacture of paper and paperboard prior to the sheetforming operation at a level not to exceed 0.015 percent by weight of the dry paper and paperboard.
Mineral oil, white	
Mono-, di-, tri-(1-methyl-1-phenylethyl)-phenol, ethoxylated, sulfated, ammonium salt with an average of 12 to 16 moles of ethylene oxide (CAS Reg. No. 68130-71-2)	For use only as an emulsifier for rosin based sizing at a level not to exceed 0.03 percent by weight of the finished dry paper and paperboard.
Monoglyceride citrate	
Monoisopropanolamine (CAS Reg. No. 78-96-6)	For use as a dispersant for titanium dioxide suspensions at a level not to exceed 0.68 percent by weight of titanium dioxide. The finished paper and paperboard will be used in contact with all food types under conditions of use E through G described in table 2 of paragraph (c) of this section.
Mustardseed oil, sulfated, ammonium, potassium, or sodium salt	
Naphthalene sulfonic acid-formaldehyde condensate, sodium salt	For use only as an adjuvant to control pulp absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet-forming operation.
Nitrocellulose, 10.9-12.2% nitrogen	
Oleic acid, sulfated, ammonium, potassium, or sodium salt	
N-Oleoyl-*N'*-stearoylethylenediamine	
Oxystearin	
Paraformaldehyde	For use only as setting agent for protein.
~~Pentanoic acid, 4,4-bis [(*gamma-omega* perfluoro-C_{8-20}-alkyl)thio] derivatives, compounds with diethanolamine (CAS Reg. No. 71608-61-2)~~	~~For use only as an oil and water repellent and used at a level not to exceed 8 pounds per ton of the finished~~

	~~paper or paperboard when such paper or paperboard is used in contact with nonalcoholic foods under conditions of use E through H described in table 2 of paragraph (c) of this section.~~
Perfluoroalkyl acrylate copolymer (CAS Reg. No. 92265-81-1) containing 35 to 40 weight percent fluorine, produced by the copolymerization of ethanaminium,*N*,*N*,*N*-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)-oxy]-, chloride; 2-propenoic acid, 2-methyl-, oxiranylmethyl ester; 2-propenoic acid, 2-ethoxyethyl ester; and 2-propenoic acid, 2<(heptadecafluoro- octyl)sulfonyl] methyl amino]ethyl ester	For use only as an oil and water repellent at a level not to exceed 0.5 percent by weight of the finished paper and paperboard in contact with nonalcoholic foods under conditions of use C, D, E, F, G, or H described in table 2 of paragraph (c) of this section.
~~Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma],[omega]-perfluoroC_{4-20}alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide~~	~~For use only as an oil and water repellant at a level not to exceed 0.44 percent perfluoroalkyl actives by weight of the finished paper and paperboard in contact with non-alcoholic foods under condition of use H as described in table 2 of paragraph (c) of this section; and in contact with food of types III, IV-A, V, VII-A, and IX described in table 1 of paragraph (c) of this section under conditions of use C through G as described in table 2 of paragraph (c) of this section.~~
Petrolatum	Complying with 178.3700 of this chapter.
Petroleum asphalt, steam and vacuum refined to meet the following specifications: Softening point 88deg. C to 93deg. C, as determined by ASTM method D36-76, "Standard Test Method for Softening Point of Bitumen (Ring-and-Ball Apparatus);" penetration at 25deg. C not to exceed 0.3 mm, as determined by ASTM method D5-73 (Reapproved 1978), "Standard Test Method for Penetration of Bituminous Materials," which are incorporated by reference (Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*); and maximum weight loss not to exceed 3% when distilled to 371deg. C, nor to exceed an additional 1.1% when further distilled between 371deg. C and thermal decomposition	For use only as a component of internal sizing of paper and paperboard intended for use in contact only with raw fruits, raw vegetables, and dry food of the type identified under Type VIII of table 1 in paragraph (c) of this section, and provided that the asphalt is used at a level not to exceed 5% by weight of the finished dry paper and paperboard fibers.
Petroleum wax, synthetic	Complying with 178.3720 of this chapter.
Phenothiazine	For use only as antioxidant in dry rosin size.
Phenyl acid phosphate	For use only as polymerization catalyst in melamine-formaldehyde modified alkyd coatings and limited to use at a level not to exceed 2% by weight of the

	coating solids.
Phenyl-[beta]-naphthylamine	For use only as antioxidant in dry rosin size and limited to use at a level not to exceed 0.4% by weight of the dry rosin size.
Phosphoric acid esters and polyesters (and their sodium salts) of triethanolamine formed by the reaction of triethanolamine with polyphosphoric acid to produce a mixture of esters having an average nitrogen content of 1.5 percent and an average phosphorus content of 32 percent (as PO_4)	For use as an adjuvant prior to the sheet forming operation to control pitch and scale formation in the manufacture of paper and paperboard intended for use in contact with food only of the types identified in paragraph (c) of this section, table 1, under Types I, IV, V, VII, VIII, and IX, and used at a level not to exceed 0.075 percent by weight of dry paper or paperboard fibers.
Poly[acrylamide-acrylic acid-*N*-(dimethyl-aminomethyl)acryl- amide], produced by reacting 2.40 to 3.12 parts by weight of polyacrylamide with 1.55 parts dimethylamine and 1 part formaldehyde, and containing no more than 0.2 percent monomer as acrylamide	For use only as a drainage aid and retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard for use in contact with fatty foods under conditions of use described in paragraph (c) of this section, table 2, conditions of use E, F, and G.
Poly(2-aminoethyl acrylate nitrate-*co*-2-hydroxypropyl acrylate) produced when one mole of hydroxypropyl acrylate and three moles of acrylic acid are reacted with three moles of ethylenimine and three moles of nitric acid, such that a 35 percent by weight aqueous solution has a minimum viscosity of 150 centipoises at 72 deg. F., as determined by RVF-series Brookfield viscometer (or equivalent) using a No. 2 spindle at 20 r.p.m	For use only as a retention and drainage aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard at a level not to exceed 0.2 percent by weight of dry paper or paperboard fiber.
Polyacrolein (1 part) -sodium bisulfite (0.7 part) adduct, containing excess bisulfite (ratio of excess bisulfite to adduct not to exceed 1.5 to 1)	For use only as an agent in modifying starches and starch gums used in the production of paper and paperboard and limited to use at a level not to exceed 0.09 mg/in^{2}of the finished paper and paperboard.
Poly[acrylamide-acrylic acid-*N*-(dimethylaminomethyl) acrylamide] (C.A. Registry No. 53800-41-2), produced by reacting 9.6-16.4 parts by weight of polyacrylamide with 1.6 parts dimethylamine and 1 part formaldehyde, and containing no more than 0.2% monomer as acrylamide, such that a 20% aqueous solution has a minimum viscosity of 4,000 cP at 25 deg. C., as determined by Brookfield viscometer model RVT, using a No. 5 spindle at 20 r/min (or equivalent method)	For use only as a drainage aid, retention aid, or dry-strength agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard at a level not to exceed 0.25 percent by weight of finished dry paper and paperboard fibers, when such paper or paperboard is used in contact with fatty foods under conditions of use described in paragraph (c) of this section, table 2, conditions of use E, F, and G.

Polyamide-epichlorohydrin modified resin produced by reacting adipic acid with diethylene triamine to produce a basic polyamide which is modified by reaction with formic acid and formaldehyde and further reacted with epichlorohydrin in the presence of ammonium hydroxide to form a water-soluble cationic resin having a nitrogen content of 13-16 percent (Kjeldahl, dry basis) such that a 35 percent by weight aqueous solution has a minimum viscosity of 75 centipoises at 25 deg. C, as determined by Brookfield viscometer using a No. 1 spindle at 12 r.p.m	For use only as a retention aid and flocculant employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 0.2 percent dry resin by weight of finished dry paper or paperboard fibers.
Polyamide-epichlorohydrin water-soluble thermosetting resins [CAS Reg. No. 68583-79-9] prepared by reacting adipic acid with diethylenetriamine to form a basic polyamide and further reacting the polyamide with an epichlorohydrin and dimethylamine mixture such that the finished resins have a nitrogen content of 17.0 to 18.0 percent of a dry basis, and that a 30-percent-by-weight aqueous solution has a minimum viscosity of 350 centipoises at 20 deg. C, as determined by a Brookfield viscometer using a No. 3 spindle at 30 r.p.m. (or equivalent method)	For use only under the following conditions:1. As a retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.12 percent by weight of dry paper or paperboard.2. The finished paper or paperboard will be used in contact with food only of the types identified in paragraph (c) of this section, table 1, under types I and IV-B and under conditions of use described in paragraph (c) of this section, table 2, conditions of use F and G.
Polyamide-epichlorohydrin water-soluble thermosetting resin (CAS Reg. No. 96387-48-3) prepared by reacting*N*-methyl-bis(3-aminopropyl) amine with oxalic acid and urea to form a basic polyamide and further reacting the polyamide with epichlorohydrin	For use only as a wet strength agent and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 1.5 percent by weight of dry paper and paperboard fibers.
Polyamide-epichlorohydrin water-soluble thermosetting resins prepared by reacting adipic acid, isophthalic acid, itaconic acid or dimethyl glutarate with diethylenetriamine to form a basic polyamide and further reacting the polyamide with one of the following:	For use only in the manufacture of paper and paperboard under conditions such that the resins do not exceed 1.5 percent by weight of the paper or paperboard.
Epichlorohydrin.	
Epichlorohydrin and ammonia mixture.	
Epichlorohydrin and sodium hydrosulfite mixture.	
Polyamidoamine-ethyleneimine-epichlorohydrin resin prepared by reacting hexanedioic acid,*N*-(2-aminoethyl)-1,2-ethanediamine, (chloromethyl)oxirane, ethyleneimine (aziridine), and polyethylene glycol, partly neutralized with sulfuric acid (CAS Reg. No. 167678-45-7)	For use only as a retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard at a level not to exceed 0.12 percent resin by weight of the finished dry paper or paperboard.
Polyamidol-epichlorohydrin modified resin produced by reacting glutaric acid dimethyl ester with diethylene-triamine to produce a basic polyamide which is modified by reaction with formaldehyde and	For use only as a wet strength agent employed prior to the sheet-forming operation in the manufacture of

further reacted with epicholorohydrin to form a water soluble cationic resin having a nitrogen content of 10.9-11.9 percent and a chlorine content of 13.8-14.8 percent, on a dry basis, and a minimum viscosity, in 12.5 percent by weight aqueous solution, of 10 centipoises at 25 deg. C, as determined by a Brookfield Model LVF viscometer using a No. 1 spindle at 60 r.p.m. (or equivalent method)	paper and paperboard, and used at a level not to exceed 2.5 percent by weight of dry paper and paperboard fibers when such paper or paperboard is used in contact with food under conditions of use E through G described in table 2 of paragraph (c) of this section.
Polyamine-epichlorohydrin resin produced by the reaction of epichlorohydrin with monomethylamine to form a prepolymer and further reaction of this prepolymer with*N,N,N',N'*-tetramethylethylenediamine such that the finished resin having a nitrogen content of 11.6 to 14.8 percent and a chlorine content of 20.8 to 26.4 percent and a minimum viscosity, in 25 percent by weight aqueous solution, of 500 centipoises at 25 deg. C, as determined by LV-series Brookfield viscometer using a No. 2 spindle at 12 r.p.m. (or by other equivalent method)	For use only as a flocculant, drainage aid, formation aid, retention aid, or strength additive employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at a level not to exceed 0.12 percent by weight of dry paper and paperboard fibers.
Polyamine-epichlorohydrin resin produced by the reaction of*N,N*-dimethyl-1,3-propanediamine with epichlorohydrin and further reacted with sulfuric acid, Chemical Abstracts Service Registry Number [27029-41-0], such that the finished resin has a maximum nitrogen content of 14.4 percent (dry basis) and a minimum viscosity in 30 percent by weight aqueous solution (pH 4-6) of 50 centipoises at 25 deg. C, as determined by Brookfield LVT model viscometer, using a No. 1 spindle at 12 r.p.m. (or equivalent method)	For use only as a clarifier in the treatment of influent water to be used in the manufacture of paper and paperboard, and used at a level not to exceed 20 parts per million of the influent water.
Polyamine-epichlorohydrin water-soluble thermosetting resin produced by reacting epichlorohydrin with: (i) polyamines comprising at least 95 percent by weight $C_4$to C_6aliphatic diamines and/or their self-condensation products, and/or (ii) prepolymers produced by reacting 1,2-dichloroethane with the polyamines in (i). The finished resin has a nitrogen content of 5.0 to 9.0 percent, a chlorine content of 18.0 to 35.0 percent on a dry basis, and a minimum viscosity, in a 25 percent by weight aqueous solution, of 50 centipoises at 20 deg. C (68 deg. F), as determined by Brookfield HAT model viscometer using a No. 1H spindle at 50 r.p.m. (or equivlent method)	For use only as a wetstrength agent and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at a level not to exceed 1 percent by weight of dry paper and paperboard fibers.
Polyamine-epichlorohydrin water-soluble thermosetting resin produced by reacting epichlorohydrin with: (i) polyamines comprising at least 95 percent by weight $C_4$to C_6aliphatic diamines and/or their seIf-condensation products and/or (ii) hexamethylenediamine, and/or (iii) bis(hexamethylene) triamine and higher homologues, and/or (iv) prepolymers produced by reacting 1,2-dichloroethane with the polyamines in (i) and/or (ii) and/or (iii). The finished resin has a nitrogen content of 5.0 to 9.0 percent, a chlorine content of 18.0 to 35.0 percent on a dry basis, and a minimum viscosity, in a 25 percent by weight aqueous solution, of 50 centipoises at 20 deg. C (68 deg. F), as determined by Brookfield HAT model viscometer using a No. 1H spindle at 50 r.p.m. (or equivalent method)	For use only as a wet-strength agent and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at a level not to exceed 1 percent by weight of dry paper and paperboard fibers.
Polyamine-epichlorohydrin water soluble thermosetting resin prepared by reacting hexamethylenediamine with 1,2-dichloroethane to form a prepolymer and further reacting this prepolymer with epichlorohydrin. This resin is then reacted with nitrilotris (methylene-phosphonic acid),	For use only as a wet-strength agent and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at

pentasodium salt, such that the finished resin has a nitrogen content of 5.0-5.3 percent; a chlorine content of 29.7-31.3 percent; and a phosphorus content of 2.0-2.2 percent, on a dry basis, and a minimum viscosity, in 25 percent by weight aqueous solution, of 50 centipoises at 25 deg. C., as determined on a Brookfield HAT model viscometer using a No. 1H spindle at 50 r.p.m. (or equivalent method)	a level not to exceed 1 percent by weight of dry paper and paperboard fibers.
Polyamine resin produced by the reaction of 1,2-dichloroethane with bis(hexamethylene)triamine and higher homologues such that the finished resin has a nitrogen content of 13.0-15.0 percent on a dry basis, and a minimum viscosity in 25-percent-by-weight aqueous solution of 75 centipoises at 25 deg. C., as determined by Brookfield HAT model viscometer using a No. 1 spindle at 50 r.p.m. (or equivalent method)	For use only as a retention aid and/or flocculent employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 0.1 percent by weight of dry paper or paperboard fibers.
Polyaminoamide-epichlorohydrin modified resin produced by reacting adipic acid with diethylenetriamine to produce a polyamide which is modified by reaction with diethylaminopropylamine and further reacted with dichloroethyl ether to form a polyamide intermediate. This polyamide intermediate is then reacted with epichlorohydrin such that the finished resins have a nitrogen content of 10.9-12.4 percent (Kjeldahl, dry basis) and a minimum viscosity in 40 percent-by-weight aqueous solution of 250 centipoises at 22 deg. C, as determined by a Brookfield Model LVT viscometer using a No. 2 spindle at 30 r.p.m. (or equivalent method)	For use only as a wet-strength agent and/or retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at a level not to exceed 0.5 percent by weight of the finished dry paper and paperboard.
Polybutene, hydrogenated; complying with the identity prescribed under 178.3740(b) of this chapter	For use only as provided in 175.300, 178.3740 and 178.3860 of this chapter.
Poly(diallyldimethylammonium chloride) (CAS Reg. No. 26062-79-3) produced by the polymerization of (diallyldimethylammonium chloride) so that the finished resin has a nitrogen content of 8.66+/-0.4 percent on a dry weight basis and a minimum viscosity in a 40 percent by weight aqueous solution of 1,000 centipoises at 25 deg. C (77 deg. F), determined by LVF Model Brookfield Viscometer using a No. 3 spindle at 30 r.p.m. (or equivalent method). The level of residual monomer is not to exceed 1 percent by weight of the polymer (dry basis)	For use only:1. As a pigment dispersant and/or retention aid prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at a level not to exceed 10 pounds of active polymer per ton of finished paper and paperboard.2. As a pigment dispersant in coatings at a level not to exceed 3.5 pounds of active polymer per ton of finished paper and paperboard.
Poly (diallyldimethylammonium chloride) (CAS Reg. No. 26062-79-3) produced by the polymerization of diallyldimethylammonium chloride so that the finished resin has a nitrogen content of 8.66+/-0.4 percent on a dry basis and a minimum viscosity in a 15 weight-percent aqueous solution of 10 centipoises at 25 deg. C (77 deg. F), as determined by LVF Model Brookfield viscometer using a No. 1 spindle at 60 r/min (or equivalent method). The level of residual monomer is not to exceed 1 weight-percent of the polymer (dry basis)	For use only as a flocculant employed prior to the sheet-forming operation in the manufacture of paper and paperboard, and used at a level not to exceed 10 mg/L (10 parts per million) of influent water.
Poly(1,2-dimethyl-5-vinylpyridinium methyl sulfate) having a nitrogen content of 5.7 to 7.3 percent and a sulfur content of 11.7 to 13.3 percent by weight on a dry basis and having a minimum viscosity in 30-percent-by-weight aqueous solution of 2,000 centipoises at 25 deg. C., as determined by LV-series Brookfield viscometer (or equivalent) using a No. 4 spindle at 60 r.p.m	For use only as an adjuvant employed in the manufacture of paper and paperboard prior to the sheet-forming operation.

Polyester resin produced by reacting dimethylolpropionic acid (CAS Registry No. 4767-03-7) as a comonomer, at no more than 30 percent by weight of total polymer solids in reaction with 2,2-dimethyl-1,3-propanediol, phthalic anhydride and isophthalic acid, such that the polyester resin has a viscosity of 200-600 centipoises at 80 deg. F as determined by a Brookfield RVT viscometer using a number 3 spindle at 50 rpm (or equivalent method)	For use only as a surface-sizing compound applied after the sheet-forming operation in the manufacture of paper and paperboard and limited to use at levels not to exceed 0.1 percent by weight of finished dry paper or paperboard.
Polyethylene, oxidized; complying with the identity prescribed in 177.1620(a) of this chapter	For use only as component of coatings that contact food only of the type identified under Type VII-B of table 1 in paragraph (c) of this section, and limited to use at a level not to exceed 50 percent by weight of the coating solids.
Polyethyleneamine mixture produced when 1 mole of ethylene dichloride, 1.05 moles of ammonia, and 2 moles of sodium hydroxide are made to react so that a 10 percent aqueous solution has a minimum viscosity of 40 centipoises at 77 deg. F, as determined by Brookfield viscometer using a No. 1 spindle at 60 r.p.m	For use only as a retention aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard.
Polyethylene glycol (200) dilaurate	For use only as an adjuvant employed in the manufacture of paper and paperboard prior to the sheet-forming operation.
Polyethylene glycol (400) dioleate	
Polyethylene glycol (400) esters of coconut oil fatty acids	
Polyethylene glycol (600) esters of tall oil fatty acids	
Polyethylene glycol (400) monolaurate	
Polyethylene glycol (600) monolaurate	
Polyethylene glycol (400) monooleate	
Polyethylene glycol (600) monooleate	
Polyethylene glycol (400) monostearate	
Polyethylene glycol (600) monostearate	
Polyethylene glycol (3,000) monostearate	
Polyethylenimine, produced by the polymerization of ethylenimine	For use only as an adjuvant employed prior to sheet formation in paper-making systems operated at a pH of 4.5 or higher, and limited to use at a level not to exceed 5% by weight of finished dry paper or paperboard fibers.
Poly(isobutene)/maleic anhydride adduct, diethanolamine reaction product. The mole ratio of	For use only as a surfactant for dispersions of

poly(isobutene)/maleic anydride adduct to diethanolamine is 1:1	polyacrylamide retention and drainage aids employed prior to the sheet formation operation in the manufacture of paper and paperboard.
Polymethacrylic acid, sodium salt, having a viscosity in 30-percent-by-weight aqueous solution of 125-325 centipoises at 25 deg. C as determined by LV-series Brookfield viscometer (or equivalent) using a No. 2 spindle at 60 r.p.m	For use only as a coating adjuvant for controlling viscosity when used at a level not to exceed 0.3% by weight of coating solids.
Polymethacrylic acid, sodium salt, having a viscosity in 40-percent-by-weight aqueous solution of 400-700 centipoises at 25 deg. C, as determined by LV-series Brookfield viscometer (or equivalent) using a No. 2 spindle at 30 r.p.m	For use only as a coating adjuvant for controlling viscosity when used at a level not to exceed 0.1% by weight of coating solids.
Poly[(methylimino)(2-hydroxytrimethylene)hydrochloride] produced by reaction of 1:1 molar ratio of methylamine and epichlorohydrin so that a 31-percent aqueous solution at 25deg. C has a Stokes viscosity range of 2.5-4.0 as determined by ASTM method D1545-76 (Reapproved; 1981), "Standard Test Method for Viscosity of Transparent Liquids by Bubble Time Method," which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*	For use only as a retention aid employed prior to the sheet-forming operation in such an amount that finished paper and paperboard will contain the additive at a level not in excess of 1 percent by weight of the dry paper and paperboard.
Poly[oxyethylene (dimethyliminio) ethylene (dimethyliminio) ethylene dichloride] produced by reacting equimolar quantities of*N,N,N,N*-tetramethylethylene-diamine and dichlorethyl ether to yield a solution of the solid polymer in distilled water at 25deg. C with a reduced viscosity of not less than 0.15 deciliter per gram as determined by ASTM method D1243-79, "Standard Test Method for -Dilute Solution Viscosity of Vinyl Chloride Polymers," which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*). The following formula is used for determining reduced viscosity:	For use only to improve dry-strength of paper and paperboard and as a retention and drainage aid employed prior to the sheet-forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.1 percent by weight of the finished dry paper and paperboard fibers.
Reduced viscosity in terms of deciliters per gram=$(t-t_0)/(t-C)$,	
where:	
t=Solution efflux time	
t_o=Water efflux time	
C=Concentration of solution in terms of grams per deciliter	
Polypropylene glycol (minimum molecular weight 1,000)	

Potassium persulfate	
2-Propenoic acid, telomer with sodium 2-methyl-2-[(1-oxo-2-propenyl)amino]-1-propane sulfonate and sodium phosphinate (CAS Reg. No. 110224-99-2)	For use only as a deposit control additive employed prior to the sheet forming operation in the manufacture of paper and paperboard and at a level not to exceed 0.15 percent by weight of the dry paper and paperboard.
Propylene glycol alginate	
Protein hydrolysate from animal hides or soybean protein condensed with oleic and/or stearic acid	
Rapeseed oil, sulfated ammonium, potassium, or sodium salt	
Ricebran oil, sulfated ammonium, potassium, or sodium salt	
Rosin and rosin derivatives	As provided in 178.3870 of this chapter.
Siloxanes (silicones), dimethyl, isopropyl methyl, methyl 1-methyl-C_{9-49}-alkyl (CAS Reg. No. 144635-08-5)	For use only as a component of polyolefin coatings with 177.1520 of this chapter at a level not to exceed 3 percent by weight. The finished coating will be used only for paper and paperboard that contact food of types VI-A and VI-B of table 1 in paragraph (c) of this section, and under conditions of use C, D, and E, as described in table 2 in paragraph (c) of this section, with a maximum hot fill temperature of 200 deg. F (94 deg. C).
Silver chloride-coated titanium dioxide	For use only as a preservative in polymer latex emulsions at a level not to exceed 2.2 parts per million (based on silver ion concentration) in the dry coating.
Sodium carboxymethyl guar gum having a minimum viscosity of 2,700 centipoises at 25 deg. C after 24 hours as determined by RV-series Brookfield viscometer (or equivalent) using a No. 4 spindle at 20 r.p.m. and using a test sample prepared by dissolving 8 grams of sodium carboxymethyl guar gum in 392 milliliters of 0.2-percent-by-weight aqueous sodium*o*-phenylphenate solution	For use only as a dry-strength and formation-aid agent employed prior to the sheet-forming operation in the manufacture of paper and paperboard and used at a level not to exceed 1% by weight of finished dry paper or paperboard fibers.
Sodium dioctyl sulfosuccinate	
Sodium formaldehyde sulfoxylate	For use only as polymerization catalyst.
Sodium hypochlorite	
Sodium*N*-methyl-*N*-oleyltaurate	For use only as an adjuvant to control pulp

	absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet-forming operation.
Sodium nitrite	For use only:1. At levels not to exceed 0.2% by weight of lubricants or release agents applied at levels not to exceed 1 lb. per ton of finished paper or paperboard.2. As an anticorrosion agent at levels not to exceed 0.2% by weight of wax emulsions used as internal sizing in the manufacture of paper and paperboard prior to the sheet-forming operation.
Sodium persulfate	
Sodium polyacrylate	For use only:1. As a thickening agent for natural rubber latex coatings, provided it is used at a level not to exceed 2 percent by weight of coating solids.2. As a pigment dispersant in coatings at a level not to exceed 0.25 percent by weight of pigment.
Sodium poly(isopropenylphosphonate) (CAS Reg. No. 118632-18-1)	For use only in paper mill boilers.
Sodium zinc potassium polyphosphate (CAS Reg. No. 65997-17-3)	For use only as a pigment dispersant in coatings at a level not to exceed 1 percent by weight of pigment.
Sperm oil, sulfated, ammonium, potassium, or sodium salt	
Stannous oleate	
Stearyl-2-lactylic acid and its calcium salt	
Styrene-butadiene copolymers produced by copolymerizing styrene-butadiene with one or more of the monomers: acrylamide, acrylic acid, fumaric acid, 2-hydroxyethyl acrylate, itaconic acid, methacrylic acid, and*N*-methylolacrylamide (CAS Reg. No. 53504-31-7). The finished copolymers shall contain not more than 10 weight percent of total polymer units derived from acrylic acid, fumaric acid, 2-hydroxyethyl acrylate, itaconic acid, and methacrylic acid, and shall contain not more than 3 weight percent of total polymer units derived from*N*-methylolacrylamide, and shall contain not more than 2 weight percent of polymer units derived from acrylamide.	
Styrene-maleic anhydride copolymer, amidated, ammonium sodium salt; having, in a 25 percent by weight aqueous solution at pH 8.8, a minimum viscosity of 600 centipoises at 25 deg. C as determined by Brookfield model LVT viscometer using a No. 3 spindle at 60 r.p.m. (or equivalent method)	For use only as a surface size at a level not to exceed 1 percent by weight of paper or paperboard substrate.
Styrene-maleic anhydride copolymer, sodium salt (minimum molecular weight 30,000)	For use only:1. As a coating thickening agent at a level not to exceed 1% by weight of coating solids.2.

	As surface size at a level not to exceed 1% by weight of paper or paperboard substrate.
Styrene-methacrylic acid copolymer, potassium salt (minimum molecular weight 30,000)	For use only as a coating thickening agent at a level not to exceed 1% by weight of coating solids.
Synthetic wax polymer prepared by the catalytic polymerization of alpha olefins such that the polymer has a maximum iodine number of 18 and a minimum number average molecular weight of 2,400	For use only as a component of petroleum wax and/or synthetic petroleum wax complying with 178.3710 or 178.3720 of this chapter at levels not to exceed 5 percent by weight of the wax:1. Under conditions of use F and G described in table 2 of paragraph (c) of this section for all foods.2. Under conditions of use E described in table 2 of paragraph (c) of this section for food Types I, II, IV-B, VI, VII-B and VIII as described in table 1 of paragraph (c) of this section.
Tallow	
Tallow alcohol	
Tallow alcohol, hydrogenated	
Tallow fatty acid, hydrogenated	
Tallow hydrogenated	
Tallow sulfated, ammonium, potassium, or sodium salt	
Tetraethylenepentamine	For use only as a modifier for amino resins.
1,4,4a,9a-Tetrahydro-9, 10-anthracenedione (CAS Reg. No. 56136-14-2)	For use only as a catalyst in the alkaline pulping of lignocellulosic materials at levels not to exceed 0.1 percent by weight of the raw lignocellulosic materials.
N,*N*,*N*',*N*'-Tetramethylethylenediamine polymer with bis-(2-chloroethyl) ether, first reacted with not more than 5 percent by weight 1-chloro-2,3-epoxypropane and then reacted with not more than 5 percent by weight poly (acrylic acid) such that a 50 percent by weight aqueous solution of the product has a nitrogen content of 4.7-4.9 percent and viscosity of 350-700 centipoises at 25 deg. C as determined by LV series Brookfield viscometer using a No. 2 spindle at 60 r.p.m. (or by other equivalent method)	For use only as a flocculent, drainage aid or retention aid employed prior to the sheet forming operation in the manufacture of paper and paperboard and limited to use at a level not to exceed 0.2 percent by weight of the finished dry paper and paperboard fibers.
Tetrasodium*N*- (1,2-dicarboxyethyl) -*N*- octadecylsulfo-succinamate	For use only as an emulsifier in aqueous dispersions of rosin sizes complying with 178.3870(a)(4) of this chapter and limited to use prior to the sheet-forming operation in the manufacture of paper and paperboard at a level not to exceed 0.02 pct by weight of finished paper and paperboard.

Triethanolamine	For use only to adjust pH during the manufacture of amino resins permitted for use as components of paper and paperboard.
Triethylene glycol adipic acid monoester produced by reacting equimolar quantities of triethylene glycol and adipic acid	For use only as a curl-control agent at a level not to exceed 2% by weight of coated or uncoated paper and paperboard.
Triethylenetetramine	For use only as a modifier for amino resins.
1,3,5-Triethylhexahydro-1,3,5-triazine (CAS Registry No. 7779-27-3)	For use only as an antimicrobial agent for coating, binder, pigment, filler, sizing, and similar formulations added prior to the heat drying step in the manufacture of paper and paperboard and limited to use at a level between 0.05 and 0.15 percent by weight of the formulation.
Undecafluorocyclohexanemethanol ester mixture of dihydrogen phosphate, compound with 2,2' iminodiethanol (1:1); hydrogen phosphate, compound with 2,2'-iminodiethanol (1:1); and P,P'-dihydrogen pyrophosphate, compound with 2,2'-iminodiethanol (1:2); where the ester mixture has a fluorine content of 48.3 pct to 53.1 pct as determined on a solids basis	For use only as an oil repellent at a level not to exceed 0.087 lb (0.046 lb of fluorine) per 1,000 ft^2 of treated paper or paperboard, as determined by analysis for total fluorine in the treated paper or paperboard without correction for any fluorine which might be present in the untreated paper or paperboard, when such paper or paperboard is used in contact with food only of the types identified in paragraph (c) of this section, table 1, under Types IVA, V, VIIA, VIII, and IX, and under the conditions of use B through G described in table 2 of paragraph (c) of this section.
Viscose rayon fibers	
Wax, petroleum	Complying with 178.3710 of this chapter.
Xanthan gum, conforming to the identity and specifications prescribed in 172.695 of this chapter, except that the residual isopropyl alcohol shall not exceed 6,000 parts per million	For use only at a maximum level of 0.125 percent by weight of finished paper as a suspension aid or stabilizer for aqueous pigment slurries employed in the manufacture of paper and paperboard.
Xylene sulfonic acid-formaldehyde condensate, sodium salt	For use only as an adjuvant to control pulp absorbency and pitch content in the manufacture of paper and paperboard prior to the sheet-forming operation.
Zeolite Na-A (CAS Reg. No. 68989-22-0)	For use as a pigment extender at levels not to exceed

	5.4 percent by weight of the finished paper and paperboard.
Zinc formaldehyde sulfoxylate	For use only as polymerization catalyst.
Zinc octoate	
Zirconium oxide	For use only as a component of waterproof coatings where the zirconium oxide is present at a level not to exceed 1 percent by weight of the dry paper or paperboard fiber and where the zirconium oxide is produced by hydrolysis of zirconium acetate.

(b) Substances identified in paragraphs (b) (1) and (2) of this section may be used as components of the food-contact surface of paper and paperboard, provided that the food-contact surface of the paper or paperboard complies with the extractives limitations prescribed in paragraph (c) of this section.
(1) Substances identified in 175.300(b)(3) of this chapter with the exception of those identified in paragraphs (b)(3) (v), (xv), (xx), (xxvi), (xxxi), and (xxxii) of that section and paragraph (a) of this section.
(2) Substances identified in this paragraph (b)(2) follow:

List of substances	**Limitations**
Acrylamide copolymerized with ethyl acrylate and/or stryene and/or methacrylic acid, subsequently reacted with formaldehyde and butyl alcohol	
Acrylamide copolymerized with ethylene and vinyl chloride in such a manner that the finished copolymers have a minimum weight average molecular weight of 30,000 and contain not more than 3.5 weight percent of total polymer units derived from acrylamide, and in such a manner that the acrylamide portion may or may not be subsequently partially hydrolyzed	For use only as coatings or components of coatings.
2-Acrylamido-2-methyl-propanesulfonic acid, homopolymer, sodium salt (CAS Reg. No. 35641-59-9)	For use only in coatings at a level not to exceed 0.01 mg/in^2
Acrylic and modified acrylic polymers	Complying with 177.1010 of this chapter.
Acrylic copolymers produced by copolymerizing 2 or more of the acrylate monomers butyl acrylate, ethyl acrylate, ethyl methacrylate, methyl acrylate, methyl methacrylate, and*n*-propyl methacrylate, or produced by copolymerizing one or more of such acrylate monomers together with one or more of the monomers acrylic acid, acrylonitrile, butadiene, 2-ethyl-hexyl acrylate, fumaric acid, glycidyl methacrylate,*n*-hexyl-methacrylate, itaconic acid, methacrylic acid, styrene, vinyl acetate, vinyl chloride, and vinylidene chloride. The finished copolymers shall contain at least 50 weight percent of polymer units derived from one or more of the monomers butyl acrylate, ethyl acrylate, ethyl methacrylate, methyl acrylate, methyl methacrylate, and*n*-propyl methacrylate; and shall contain not more than 5 weight percent of total polymer units derived from acrylic acid, fumaric acid, glycidyl methacrylate,*n*-hexyl methacrylate, itaconic acid, and methacrylic acid. The provision limiting the finished acrylic copolymers to not more	

than 5 units derived from acrylic acid, fumaric acid, glycidyl methacrylate,*n*-hexyl methacrylate, itaconic acid, and methacrylic acid is not applicable to finished acrylic copolymers used as coating adjuvants at a level not exceeding 2 weight percent of total coating solids	
Alkyl mono- and disulfonic acids, sodium salts (produced from*n*-alkanes in the range of C_{10}-$C_{18}$with not less than 50 percent C_{14}-C_{16}).	For use only:1. As emulsifiers for vinylidene chloride copolymer coatings and limited to use at levels not to exceed 2 percent by weight of the coating solids.2. As emulsifiers for vinylidene chloride copolymer or homopolymer coatings at levels not to exceed a total of 2.6 percent by weight of coating solids. The finished polymer contacts food only of types identified in paragraph (c) of this section, table 1, under Types I, II, III, IV, V, VIA, VIB, VII, VIII, and IX and under conditions of use E, F, and G described in table 2 of paragraph (c) of this section.
2-Bromo-4'-hydroxyacetophenone	For use only as a preservative for coating formulations, binders, pigment slurries, and sizing solutions at a level not to exceed 0.006 percent by weight of the coating, solution, slurry or emulsion.
Butanedioic acid, sulfo-1,4-di-(C_9-C_{11}alkyl) ester, ammonium salt (also known as butanedioic acid, sulfo-1,4-diisodecyl ester, ammonium salt [CAS Reg. No. 144093-88-9]).	For use as a surface active agent in package coating inks at levels not to exceed 3 percent by weight of the coating ink.
Butylbenzyl phthalate	Complying with 178.3740 of this chapter.
Butyl oleate, sulfated, ammonium, potassium, or sodium salt	
Butyraldehyde	
Captan (*N*-trichloromethylmercapto-4-cyclohexene-1, 2-dicarboximide)	For use only as a mold- and mildew-proofing agent in coatings intended for use in contact with food only of the types identified in paragraph (c) of this section, table 1, under Type I, II, VI-B, and VIII.
Castor Oil, polyoxyethylated (42 moles ethylene oxide)	For use only as an emulsifier in nitrocellulose coatings for paper and paperboard intended for use in contact with food only of the types identified in paragraph (c) of this section, table 1, under Types IV A, V, VII A, VIII, and IX; and limited to use at a level not to exceed 8 percent by weight of the coating solids.
1-(3-Chloroallyl)-3,5,7-triaza-1- azoniaadamantane chloride (CAS Reg. No. 4080-31-3)	For use only:1. As a preservative at a level of 0.3

	weight percent in latexes used as pigment binders in paper and paperboard intended for use in contact with nonacidic, nonalcoholic food and under the conditions of use described in paragraph (c) of this section, table 2, conditions of use E, F, and G.2. As a preservative at a level not to exceed 0.07 weight percent in latexes and 0.05 weight percent in pigment slurries used as components of coatings for paper and paperboard intended for use in contact with food.
5-Chloro-2-methyl-4-isothiazolin-3-one (CAS Reg. No. 26172-55-4) and 2-methyl-4-isothiazolin-3-one (CAS Reg. No. 2682-20-4) mixture at a ratio of 3 parts to 1 part, manufactured from methyl-3-mercaptopropionate (CAS Reg. No. 2935-90-2). The mixture may contain magnesium nitrate (CAS Reg. No. 10377-60-3) at a concentration equivalent to the isothiazolone active ingredients (weight/weight)	For use only:1. As an antimicrobial agent for polymer latex emulsions in paper coatings at a level not to exceed 50 parts per million (based on isothiazolone active ingredients) in the coating formulation.2. As an antimicrobial agent for finished coating formulations and for additives used in the manufacture of paper and paperboard including fillers, binders, pigment slurries, and sizing solutions at a level not to exceed 25 parts per million (based on isothiazolone active ingredients) in the coating formulations and additives.
Copper 8-quinolinolate	For use only as preservative for coating formulations.
Cyclized rubber produced when natural pale crepe rubber dissolved in phenol is catalytically cyclized so that the finished cyclized rubber has a melting point of 145 deg. C to 155 deg. C as determined by ASTM method E28-67 (Reapproved 1982), "Standard Test Method for Softening Point by Ring-and-Ball Apparatus," which is incorporated by reference (Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*), and contains no more than 4000 ppm of residual-free phenol as determined by a gas liquid chromatographic procedure titled "Determination of Free Phenol in Cyclized Rubber Resin," which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*	For use only in coatings for paper and paperboard intended for use in contact with food only of the types identified in paragraph (c) of this section, table 1, under Types VIII and IX.

1,2-Dibromo-2,4-dicyanobutane (CAS Reg. No. 35691-65-7)	For use only as a preservative at levels not more than 0.05 weight percent and not less than 0.01 weight percent: in latexes used as pigment binders in coatings; in pigment slurries used in coatings; and/or in coatings themselves. The total level of the preservative in the finished coating shall not exceed 0.04 weight percent of the finished coating solids.
Dibutyl phthalate	
Dibutyl sebacate	
Di(C_7,C_9-alkyl) adipate	Complying with 178.3740 of this chapter.
Dicyclohexyl phthalate	
Diethylene glycol dibenzoate (CAS Reg. No. 120-55-8)	For use only as a plasticizer for polyvinyl acetate coatings at a level not to exceed 5 percent by weight of the coating solids under conditions described in paragraph (c) of this section, table 2, conditions of use E, F, and G.
Diethylene glycol ester of the adduct of terpene and maleic anhydride	
Dihydroxy dichlorodiphenyl methane	For use only as preservative for coating formulations.
Dimethylpolysiloxane, 100 centistokes viscosity	
Dimethylpolysiloxane-beta-phenylethyl methyl polysiloxane copolymer (2:1), 200 to 400 centistokes viscosity	
N,*N'*-Diphenyl-*p*-phenylenediamine	For use only as polymerization inhibitor in 2-sulfoethyl methacrylate, sodium salt.
Dipropylene glycol dibenzoate (CAS Reg. No. 27138-31-4)	1. For use only as a plasticizer for polyvinyl acetate coatings at a level not to exceed 5 percent by weight of the coating solids under conditions described in paragraph (c) of this section, table 2, condition of use E.2. For use only as a plasticizer for polyvinyl acetate coatings at a level not to exceed 10 percent by weight of the coating solids under conditions described in paragraph (c) of this section, table 2, conditions of use F and G.
Disodium*N*-octadecylsulfosuccinamate	For use only as an emulsifier in resin latex coatings and limited to use at a level not to exceed 0.05% by

	weight of the coating solids.
EDTA (ethylenediaminetetraacetic acid) and its sodium and/or calcium salts	
Ethanedial, polymer with tetrahydro-4-hydroxy-5-methyl-2(1H)pyrimidinone, propoxylated (CAS Reg. No. 118299-90-4)	For use only as an insolubilizer for starch-based coatings and limited to use at a level not to exceed 5.0 percent by weight of the coating.
Ethylene-acrylic acid copolymers produced by the copolymerization of ethylene and acrylic acid and/or their partial ammonium salts. The finished copolymer shall contain no more than 25 weight percent of polymer units derived from acrylic acid and no more than 0.35 weight percent of residual monomeric acrylic acid, and have a melt index not to exceed 350 as determined by ASTM method D1238-82, "Standard Test Method for Flow Rates of Thermoplastics by Extrusion Plastometer," which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*	
Formaldehyde	For use only as preservative for coating formulations.
Glyoxal	For use only as an insolubilizing agent in starch- and protein-based coatings that contact nonalcoholic foods, and limited to use at a level not to exceed 6 percent by weight of the starch or protein fraction of the coating solids.
Glyceryl monobutyl ricinoleate	
Hydroxymethyl derivatives (mixture of mono and poly) of [N-(1, 1-dimethyl-3-oxobutyl) acrylamide] produced by reacting 1 mole of the [N-(1,1-dimethyl-3-oxobutyl) acrylamide] with 3 moles of formaldehyde such that the finished product has a maximum nitrogen content of 6.2 percent and a maximum hydroxyl content of 15 percent by weight on a dry basis	For use only as a comonomer in polyvinyl acetate latex coatings and limited to use at a level not to exceed 1 percent by weight of dry polymer solids.
Isobutyl oleate, sulfated, ammonium, potassium, or sodium salt	
Maleic anhydride adduct of butadiene-styrene copolymer	
[alpha]-Methylstyrene-vinyltoluene copolymer resins (molar ratio 1[alpha]-methylstyrene to 3 vinyltoluene)	
Modified kaolin clay (CAS Reg. No. 1344-00-9) is produced by the reaction of sodium silicate (CAS Reg. No. 1344-09-8) and kaolinite clay (CAS Reg. No. 1332-58-7) under hydrothermal conditions. The reaction product has a molecular weight between 246 and 365 and consists of 46 to 55 percent silicon dioxide ($Si0_2$), 28 to 42 percent aluminum oxide ($A1_20_3$), and 2 to 7 percent	For use only as a component of coatings in paper and paperboard products at a level not to exceed 9 percent by weight of the coating intended for use in contact with food of Types I through IX described in table 1 of

of sodium oxide (Na_20). The reaction product will not consist of more than 70 percent modified kaolin clay	paragraph (c) of this section under conditions of use C through H described in table 2 of paragraph (c) of this section.
Naphthalene sulfonic acid-formaldehyde condensate, sodium salt	
Oleyl alcohol	
Oxazolidinylethylmethacrylate (CAS Registry No. 46236-15-1) copolymer with ethyl acrylate and methyl methacrylate, and containing not more than 6 percent by weight of oxazolidinylethylmethacrylate. Maximum nitrogen content shall be 0.5 percent and number average molecular weight of that portion of the copolymer soluble in tetrahydrofuran shall be not less than 50,000	For use only as a binder for pigment coatings as a binder level not to exceed 4.0 percent by weight of dry paper or paperboard.
Pentaerythritol tetrastearate	
Petroleum alicyclic hydrocarbon resins, or the hydrogenated product thereof, meeting the following specifications: Softening point 97 deg. C minimum, as determined by ASTM method E28-67 (Reapproved 1982), "Standard Test Method for Softening Point by Ring and Ball Apparatus;" aniline point 120 deg. C minimum, as determined by ASTM method D611-82, "Standard Test Methods for Aniline Point and Mixed Aniline Point of Petroleum Products and Hydrocarbon Solvents," which are incorporated by reference (Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*). Specific gravity 0.96-0.99 (20 deg. C/20 deg. C). Such petroleum hydrocarbon resins are produced by the catalytic polymerization of dienes and olefins from low-boiling distillates of cracked petroleum stocks that contain no material boiling over 200 deg. C and that meet the ultraviolet absorbance limits prescribed in 172.880(b) of this chapter when subjected to the analytical procedure described in 172.886(b) of this chapter, modified as follows: Treat the product as in the first paragraph under "Procedure" in 172.250(b)(3) of this chapter. Then proceed with 172.886(b) of this chapter, starting with the paragraph commencing with "Promptly complete transfer of the sample * * *"	For use only as modifiers in waxpolymer blend coatings for corrugated paperboard intended for use in bulk packaging or raw fruits, raw vegetables, iced meat, iced fish, and iced poultry; and limited to use at a level not to exceed 30 weight-percent of the coating solids.
Polyester resin formed by the reaction of the methyl ester of rosin, phthalic anhydride, maleic anhydride and ethylene glycol, such that the polyester resin has an acid number of 4 to 11, a drop-softening point of 70 deg. C-92 deg. C., and a color of K or paler	
Polyester resin produced by reacting the acid groups in montan wax with ethylene glycol	
Polyethylene, oxidized	Complying with 177.1620 of this chapter.
Polyethylene reacted with maleic anhydride such that the modified polyethylene has a	

saponification number not in excess of 6 after Soxhlet extraction for 24 hours with anhydrous ethyl alcohol	
Polyoxyethylated (40 moles) tallow alcohol sulfate, sodium salt	Not to exceed 300 p.p.m. in finished coated paper or paperboard.
Polyoxypropylene-polyoxyethylene block polymers (minimum molecular weight 6,800)	
Polyvinyl acetate	
Polyvinyl alcohol (minimum viscosity of 4% aqueous solution at 20 deg. C. of 4 centipoises)	
Polyvinyl butyral	
Polyvinyl formal	
Polyvinylidene chloride	
Polyvinyl pyrrolidone	
Polyvinyl stearate	
Propylene glycol mono- and diesters of fats and fatty acids	
Siloxanes and silicones; platinum-catalyzed reaction product of vinyl-containing dimethyl polysiloxane (CAS Reg. Nos. 68083-19-2 and 68083-18-1) with methyl hydrogen polysiloxane (CAS Reg. No. 63148-57-2) or dimethyl (methyl hydrogen) polysiloxane (CAS Reg. No. 68037-59-2). Diallyl maleate (CAS Reg No. 999-21-3), dimethyl maleate (CAS Reg. No. 624-48-6), 1-ethynyl-1-cyclohexanol (CAS Reg. No. 78-27-3) and vinyl acetate (CAS Reg. No. 108-05-4) may be used as optional polymerization inhibitors	For use only as a surface coating. Platinum content not to exceed 200 parts per million.1. In coatings for paper and paperboard provided the coating contacts food only of the types identified in paragraph (c) of this section, table 1, under Types I, II, VI, and VII-B when used under conditions of use E, F, and G described in table 2 of paragraph (c) of this section.2. In coatings for paper and paperboard provided the coating contacts food only of the types identified in paragraph (c) of this section, table 1, under Types III, IV, V, VII-A, VIII, and IX when used under conditions of use A through H described in table 2 of paragraph (c) of this section.
Siloxanes and silicones; platinum-catalyzed reaction product of vinyl-containing dimethylpolysiloxane (CAS Reg. Nos. 68083-19-2 and 68083-18-1), with methyl hydrogen polysiloxane (CAS Reg. No. 63148-57-2). Dimethyl maleate (CAS Reg. No. 624-48-6), vinyl acetate (CAS Reg. No. 108-05-4), dibutyl maleate (CAS Reg. No. 105-76-0) and diallyl maleate (CAS Reg. No. 999-21-3) may be used as optional polymerization inhibitors. The polymer may also contain C_{16}-C_{18}olefins (CAS Reg. No. 68855-60-7) as a control release agent	Platinum content not to exceed 100 parts per million. For use only as a release coating for pressure sensitive adhesives.
Sodium decylbenzenesulfonate	

Sodium dihexyl sulfosuccinate	
Sodium*n*-dodecylpolyethoxy (50 moles) sulfate-sodium isododecylphenoxypolyethoxy (40 moles) sulfate mixtures	For use only as an emulsifier in coatings that contact food only of the types identified in paragraph (c) of this section, table 1, under Types IV-A, V, VII, VIII, and IX; and limited to use at levels not to exceed 0.75 percent by weight of the coating solids.
Sodium 2-ethylhexyl sulfate	
Sodium oleoyl isopropanolamide sulfosuccinate	
Sodium pentachlorophenate	For use only as preservative for coating formulations.
Sodium*o*-phenylphenate	Do.
Sodium vinyl sulfonate polymerized	
Sodium xylenesulfonate (CAS Reg. No. 1300-72-7)	For use only in paper and paperboard coatings at levels not to exceed 0.01 percent by weight of the finished paper and paperboard.
Styrene copolymers produced by copolymerizing styrene with maleic anhydride and its methyl and butyl (*sec*- or*iso*-) esters. Such copolymers may contain [beta]-nitrostyrene as a polymerization chain terminator	For use only as a coating or component of coatings and limited to use at a level not to exceed 1% by weight of paper or paperboard substrate.
Styrene polymers made by the polymerization of any combination of styrene or alpha methyl styrene with acrylic acid, methacrylic acid, 2-ethyl hexyl acrylate, methyl methacrylate, and butyl acrylate. The styrene and alpha methyl styrene, individually, may constitute from 0 to 80 weight percent of the polymer. The other monomers, individually, may be from 0 to 40 weight percent of the polymer. The polymer number average molecular weight (M_n) shall be at least 2,000 (as determined by gel permeation chromatography). The acid number of the polymer shall be less than 250. The monomer content shall be less than 0.5 percent	For use only in contact with foods of Types IV-A, V, and VII in table 1 of paragraph (c) of this section, under use conditions E through G in table 2 of paragraph (c), and with foods of Types VIII and IX without use temperature restriction.
Styrene-acrylic copolymers (CAS Reg. No. 25950-40-7 produced by polymerizing 77 to 83 parts by weight of styrene with 13 to 17 parts of methyl methacrylate, 3 to 4 parts of butyl methacrylate, 0.5 to 2.5 parts of methacrylic acid, and 0.1 to 0.3 part of butyl acrylate such that the finished copolymers have a minimum number average molecular weight greater than 100,000 and a level of residual styrene monomer in the polymer not to exceed 0.1 percent by weight	For use only as a component of coatings and limited to use at a level not to exceed 20 percent by weight of the coating solids.
Styrene-butadiene copolymers produced by copolymerizing styrene-butadiene with one or more of the monomer: acrylamide, acrylic acid, fumaric acid, 2-hydroxyethyl acrylate, itaconic acid, and methacrylic acid. The finished copolymers shall contain not more than 10 weight percent of total polymer units derived from acrylic acid, fumaric acid, 2-hydroxyethyl acrylate, itaconic acid and methacrylic acid, and shall contain not more than 2 weight percent of polymer units derived	

from acrylamide	
Styrene-butadiene copolymers with 2-hydroxyethyl acrylate and acrylic acid containing not more than 15 weight percent acrylic acid and no more than 20 weight percent of a combination of 2-hydroxyethyl acrylate and acrylic acid	
Styrene-butadiene-vinylidene chloride copolymers containing not more than 40 weight percent of vinylidene chloride in the finished copolymers. The finished copolymers may contain not more than 10 weight percent of total polymer units derived from acrylic acid, fumaric acid, 2-hydroxyethyl acrylate, itaconic acid, and/or methacrylic acid	For use only as coatings or components of coatings.
Styrene-dimethylstyrene-[alpha]-methylstyrene copolymers produced by polymerizing equimolar ratios of the three comonomers such that the finished copolymers have a minimum average molecular weight of 835 as determined by ASTM method D2503-82, "Standard Test Method for Molecular Weight (Relative Molecular Mass) of Hydrocarbons by Thermoelectric Measurement of Vapor Pressure," which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*	For use only in coatings for paper and paperboard intended for use in contact with nonfatty food and limited to use at a level not to exceed 50% by weight of the coating solids.
Styrene-isobutylene copolymers (weight average molecular weight not less than 6,300)	For use only in coatings for paper and paperboard intended for use in contact under conditions of use D G described in table 2 of paragraph (c) of this section, with food of Types I, II, IV-B, VI-B, VII-B, and VIII described in table 1 of paragraph (c) of this section; and limited to use at a level not to exceed 40 percent by weight of the coating solids.
Styrene-maleic anhydride copolymers	For use only as a coating or component of coatings and limited for use at a level not to exceed 2 percent by weight of paper or paperboard substrate.
Styrene-methacrylic acid copolymers containing no more than 5 weight percent of polymer units derived from methacrylic acid	
Styrene-vinylidene chloride copolymers containing not more than 40 weight percent of vinylidene chloride in the finished copolymers. The finished copolymers may contain not more than 5 weight percent of total polymer units derived from acrylic acid, fumaric acid, itaconic acid, and/or methacrylic acid	For use only as coatings or components of coatings.
2-Sulfoethyl methacrylate, sodium salt [Chemical Abstracts Service No. 1804-87-1]	For use only in copolymer coatings under conditions of use E, F, and G described in paragraph (c) of this section,

	table 2, and limited to use at a level not to exceed 2.0 percent by weight of the dry copolymer coating.
[alpha]<[em>p-(1,1,3,3-Tetramethylbutyl) phenyl]-*omega*-hydroxypoly (oxyethylene) hydrogen sulfate, sodium salt mixture with [alpha]-<[em>p-(1,1,3,3-tetramethylbutyl)-phenyl]-*omega*-hydroxypoly (oxyethylene) with both substances having a poly(oxyethylene) content averaging 3 moles	For use only as a surface-active agent at levels not to exceed 3 percent by weight of vinyl acetate polymer with ethylene and*N*-(hydroxymethyl) acrylamide intended for use in coatings for paper and paperboard intended for use in contact with foods:1. Of the types identified in paragraph (c) of this section, table 1, under Types I, II, III, IV, VI-B, and VII, and under the conditions of use described in paragraph (c) of this section, table 2, conditions of use E, F, and G.2. Of the types identified in paragraph (c) of this section, table 1, under Types V, VIII and IX and under the conditions of use described in paragraph (c) of this section, table 2, conditions of use C, D, E, F, and G.
Tetrasodium*N*-(1,2-dicarboxyethyl)-*N*-octadecylsulfo-succinamate	For use only as an emulsifier in resin latex coatings, and limited to use at a level not to exceed 0.05% by weight of the coating solids.
Toluenesulfonamide-formaldehyde resins	
Vinyl acetate copolymers produced by copolymerizing vinyl acetate with one or more of the monomers acrylamide, acrylic acid, acrylonitrile, bicyclo-[2.2.1]*hept*-2-ene-6-methylacrylate, butyl acrylate, crotonic acid, decyl acrylate, diallyl fumarate, diallyl maleate, diallyl phthalate, dibutyl fumarate, dibutyl itaconate, dibutylmaleate, di(2-ethylhexyl) maleate, divinyl benzene, ethyl acrylate, 2-ethyl-hexyl acrylate, fumaric acid, itaconic acid, maleic acid, methacrylic acid, methyl acrylate, methyl methacrylate, mono(2-ethylhexyl) maleate, monoethyl maleate, styrene, vinyl butyrate, vinyl crotonate, vinyl hexoate, vinylidene chloride, vinyl pelargonate, vinyl propionate, vinyl pyrrolidone, vinyl stearate, and vinyl sulfonic acid. The finished copolymers shall contain at least 50 weight percent of polymer units derived from vinyl acetate and shall contain no more than 5 weight percent of total polymer units derived from acrylamide, acrylic acid, crotonic acid, decyl acrylate, dibutyl itaconate, di(2-ethylhexyl) maleate, fumaric acid, itaconic acid, maleic acid, methacrylic acid, mono(2-ethylhexyl) maleate, monoethyl maleate, vinyl butyrate, vinyl hexoate, vinyl pelargonate, vinyl propionate, vinyl stearate, and vinyl sulfonic acid	
Vinyl acetate polymer with ethylene and*N*-(hydroxymethyl) acrylamide containing not more than 6 weight percent of total polymer units derived from*N*-(hydroxymethyl) acrylamide	For use only in coatings for paper and paperboard intended for use in contact with foods:1. Of the types identified in paragraph (c) of this section,

	table 1, under Types I, II, III, IV, VI B, and VII and under the conditions of use described in paragraph (c) of this section, table 2, conditions of use E, F, and G.2. Of the types identified in paragraph (c) of this section, table 1, under Types V, VIII, and IX and under the conditions of use described in paragraph (c) of this section, table 2, conditions of use C, D, E, F, and G.
Vinyl chloride copolymers produced by copolymerizing vinyl chloride with one or more of the monomers acrylonitrile; fumaric acid and its methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, or octyl esters; maleic acid and its methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, or octyl esters; maleic anhydride; 5-norbornene-2, 3-dicarboxylic acid, mono-*n*-butyl ester; vinyl acetate-and vinylidene chloride. The finished copolymers shall contain at least 50 weight percent of polymer units derived from vinyl chloride: shall contain no more than 5 weight percent of total polymer units derived from fumaric and/or maleic acid and/or their methyl, ethyl, propyl, butyl, amyl, heptyl, or octyl monoesters or from maleic anhydride or from mono-*n*-butyl ester of 5-norbornene-2, 3-dicarboxylic acid (however, in any case the finished copolymers shall contain no more than 4 weight percent of total polymer units derived from mono-*n*-butyl ester of 5-norbornene-2,3-dicarboxylic acid)	
Vinyl chloride-vinyl acetate hydroxyl-modified copolymers	
Vinyl chloride-vinyl acetate hydroxyl-modified copolymers reacted with trimellitic anhydride	
Vinylidene chloride copolymers produced by copolymerizing vinylidene chloride with one or more of the monomers acrylamide acrylic acid, acrylonitrile, butyl acrylate, butyl methacrylate ethyl acrylate, ethyl methacrylate, fumaric acid, itaconic acid, methacrylic acid, methyl acrylate, methyl methacrylate, octadecyl methacrylate, propyl acrylate, propyl methacrylate, vinyl chloride and vinyl sulfonic acid. The finished copolymers shall contain at least 50 weight percent of polymer units derived from vinylidene chloride; and shall contain no more than 5 weight percent of total polymer units derived from acrylamide, acrylic acid, fumaric acid, itaconic acid, methacrylic acid, octadecyl methacrylate, and vinyl sulfonic acid	
Colorants:	
Aluminum	For use as a colorant only.
Aluminum hydrate	Do.
Aluminum and potassium silicate (mica)	Do.
Aluminum mono-, di-, and tristearate	Do.

Aluminum silicate (China clay)	Do.
Barium sulfate	Do.
Bentonite	Do.
Bentonite, modified with dimethyldioctadecylammonium ion	Do.
Burnt umber	Do.
Calcium carbonate	Do.
Calcium silicate	Do.
Calcium sulfate	Do.
Carbon black (channel process)	Do.
Cobalt aluminate	Do.
Diatomaceous earth	Do.
Iron oxides	Do.
Magnesium oxide	Do.
Magnesium silicate (talc)	Do.
Phthalocyanine blue (C.I. pigment blue 15, 15:1, 15:2, 15:3, and 15:4; C.I. No. 74160; CAS Reg. No. 147-14-8)	Do.
Raw sienna	Do.
Silica	Do.
Tartrazine lake (certified FD+C Yellow No. 5 only)	Do.
Titanium dioxide	Do.
Titanium dioxide-barium sulfate	Do.
Titanium dioxide-magnesium	Do.
silicate	
Zinc carbonate	Do.
Zinc oxide	Do.

(c) The food-contact surface of the paper and paperboard in the finished form in which it is to contact food, when extracted with the solvent or solvents characterizing the type of food, and under conditions of time and temperature characterizing the conditions of its intended use as determined from tables 1 and 2 of this paragraph, shall yield net chloroform-soluble extractives (corrected for wax, petrolatum, mineral oil and zinc extractives as zinc oleate) not to exceed 0.5 milligram per square inch of food-contact surface as determined by the methods described in paragraph (d) of this section.

Table 1--Types of Raw and Processed Foods

I. Nonacid, aqueous products; may contain salt or sugar or both (pH above 5.0).
II. Acid, aqueous products; may contain salt or sugar or both, and including oil-in-water emulsions of low- or high-fat content.
III. Aqueous, acid or nonacid products containing free oil or fat; may contain salt, and including water-in-oil emulsions of low- or high-fat content.
IV. Dairy products and modifications:
    A. Water-in-oil emulsions, high- or low-fat.
    B. Oil-in-water emulsions, high- or low-fat.
    V. Low-moisture fats and oil.
VI. Beverages:
    A. Containing up to 8 percent of alcohol.
    B. Nonalcoholic.
    C. Containing more than 8 percent alcohol.
VII. Bakery products other than those included under Types VIII or IX of this table:
    A. Moist bakery products with surface containing free fat or oil.
    B. Moist bakery products with surface containing no free fat or oil.
VIII. Dry solids with the surface containing no free fat or oil (no end test required).
IX. Dry solids with the surface containing free fat or oil.

Table 2--Test Procedures with Time Temperature Conditions for Determining Amount of Extractives From the Food-Contact Surface of Uncoated or Coated Paper and Paperboard, Using Solvents Simulating Types of Foods and Beverages

Condition of use	Types of food (see table 1)	Food-simulating solvents			
		Water	Heptane[1]	8 percent alcohol	50 percent alcohol
		Time and temperature	Time and temperature	Time and temperature	Time and temperature
A. High temperature heat-sterilized (e.g., over 212 deg. F)	I, IV-B, VII-B	250 deg. F, 2 hr			
	III, IV-A, VII-A	.....do	150 deg. F, 2 hr		
B. Boiling water sterilized	II, VII-B	212 deg. F, 30 min			
	III, VII-A	.....do	120 deg. F, 30 min		
C. Hot filled or pasteurized above 150 deg. F	II, IV-B, VII-B	Fill boiling, cool to 100 deg. F			
	III, IV-A, VII-A	.....do	120 deg. F, 15 min		
	V, IX		.....do		

D. Hot filled or pasteurized below 150 deg. F	II, IV-B, VI-B,				
	VII-B	150 deg. F, 2 hr			
	III, IV-A, VII-A	.....do	100 deg. F, 30 min		
	V, IX		.....do		
	VI-A			150 deg. F, 2 hr	
	VI-C				150 deg. F, 2 hr.
E. Room temperature filled and stored (no thermal treatment in the container)	I, II, IV-B, VI-B, VII-B	120 deg. F, 24 hr			
	III, IV-A, VII-A	.....do	70 deg. F, 30 min		
	V, IX		.....do		
	VI-A			120 deg. F, 24 hr	
	VI-C				120 deg. F, 24 hr.
F. Refrigerated storage (no thermal treatment in the container)	III, IV-A, VII-A	70 deg. F, 48 hr	70 deg. F, 30 min		
	I, II, IV-B, VI-B, VII-B	.....do			
	VI-A			70 deg. F, 48 hr	
	VI-C				70 deg. F, 48 hr.
G. Frozen storage (no thermal treatment in the container)	I, II, IV-B, VII-B	70 deg. F, 24 hr			
	III, VII-A	.....do	70 deg. F, 30 min		
H. Frozen or refrigerated storage: Ready-prepared foods intended to be reheated in container at time of use:					
1. Aqueous or oil-in-water emulsion of high- or low-fat	I, II, IV-B, VII-B	212 deg. F, 30 min			
2. Aqueous, high- or low-free oil or fat	III, IV-A, VII-A, IX	.....do	120 deg. F, 30 min		

[1]Heptane extractability results must be divided by a factor of five in arriving at the extractability for a food product having water-in-oil emulsion or free oil or fat. Heptane food-simulating solvent is not required in the case of wax-polymer blend coatings for corrugated paperboard containers intended for use in bulk packaging of iced meat, iced fish, and iced poultry.

(d)*Analytical methods* --

(1)*Selection of extractability conditions.* First ascertain the type of food product (table 1, paragraph (c) of this section) that is being packed commercially in the paper or paperboard and the normal conditions of thermal treatment used in packaging the type of food involved. Using table 2, paragraph (c) of this section, select the food-simulating solvent or solvents and the time-temperature exaggerations of the paper or paperboard use conditions. Having selected the appropriate food-simulating solvent or solvents and the time-temperature exaggeration over normal use, follow the applicable extraction procedure.

(2)*Reagents* --(i)*Water.* All water used in extraction procedures should be freshly demineralized (deionized) distilled water.

(ii)*n-Heptane.* Reagent grade, freshly redistilled before use, using only material boiling at 208 deg. F.

(iii)*Alcohol.* 8 or 50 percent (by volume), prepared from undenatured 95 percent ethyl alcohol diluted with demineralized (deionized) distilled water.

(iv)*Chloroform.* Reagent grade, freshly redistilled before use, or a grade having an established consistently low blank.

(3)*Selection of test method.* Paper or paperboard ready for use in packaging shall be tested by use of the extraction cell described in "Official Methods of Analysis of the Association of Official Analytical Chemists," 13th Ed. (1980), sections 21.010-21.015, under "Exposing Flexible Barrier Materials for Extraction," which is incorporated by reference (Copies may be obtained from the AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*); also described in ASTM method F34-76 (Reapproved 1980), "Standard Test Method for Liquid Extraction of Flexible Barrier Materials," which is incorporated by reference (copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*), except that formed paper and paperboard products may be tested in the container by adapting the in-container methods described in 175.300(e) of this chapter. Formed paper and paperboard products such as containers and lids, that cannot be tested satisfactorily by any of the above methods may be tested in specially designed extraction equipment, usually consisting of clamping devices that fit the closure or container so that the food-contact surface can be tested, or, if flat samples can be cut from the formed paper or paperboard products without destroying the integrity of the food-contact surface, they may be tested by adapting the following "sandwich" method:

(i)*Apparatus.* (*a*) Thermostated (+/-1.0 deg. F) water bath, variable between 70 deg. F and 120 deg. F water bath cover capable of holding at least one 800-milliliter beaker partially submersed in bath.

(*b*) Analytical balance sensitive to 0.1 milligram with an approximate capacity of 100 grams.

(*c*) Tongs.

(*d*) Hood and hot-plate facilities.

(*e*) Forced draft oven.

For each extraction, the following additional apparatus is necessary:

(*f*) One No. 2 paper clip.

(*g*) One 800-milliliter beaker with watch-glass cover.

(*h*) One 250-milliliter beaker.

(*i*) Five 21/2-inch-square aluminum screens (standard aluminum window screening is acceptable).

(*j*) One wire capable of supporting sample stack.

(ii)*Procedure.* (*a*) For each extraction, accurately cut eight 21/2-inch-square samples from the formed paper or paperboard product to be tested.
(*b*) Carefully stack the eight 21/2-inch-square samples and the five 21/2-inch-square aluminum screens in sandwich form such that the food-contact side of each sample is always next to an aluminum screen, as follows: Screen, sample, sample, screen, sample, sample, screen, etc. Clip the sandwich together carefully with a No. 2 paper clip, leaving just enough space at the top to slip a wire through.
(*c*) Place an 800-milliliter beaker containing 100-milliliters of the appropriate food-simulating solvent into the constant temperature bath, cover with a watch glass and condition at the desired temperature.
(*d*) After conditioning, carefully lower the sample sandwich with tongs into the beaker.
(*e*) At the end of the extraction period, using the tongs, carefully lift out the sample sandwich and hang it over the beaker with the wire.
(*f*) After draining, pour the food-simulating solvent solution into a tared 250-milliliter beaker. Rinse the 800-milliliter beaker three times, using a total of not more than 50 milliliters of the required solvent.
(*g*) Determine total nonvolatile extractives in accordance with paragraph (d)(5) of this section.
(4)*Selection of samples.* Quadruplicate samples should be tested, using for each replicate sample the number of cups, containers, or preformed or converted products nearest to an area of 100 square inches.
(5)*Determination of amount of extractives* --(i)*Total residues.* At the end of the exposure period, remove the test container or test cell from the oven and combine the solvent for each replicate in a clean Pyrex (or equivalent) flask or beaker being sure to rinse the test container or cell with a small quantity of clean solvent. Evaporate the food-simulating solvents to about 100 milliliters in the flask or beaker, and transfer to a clean, tared evaporating dish (platinum or Pyrex), washing the flask three times with small portions of solvent used in the extraction procedure, and evaporate to a few milliliters on a nonsparking, low-temperature hotplate. The last few milliliters should be evaporated in an oven maintained at a temperature of approximately 221 deg. F. Cool the evaporating dish in a desiccator for 30 minutes and weigh the residue to the nearest 0.1 milligram, (*e*). Calculate the extractives in milligrams per square inch of the container or sheeted paper or paperboard surface.
(*a*)*Water and 8- and 50-percent alcohol.* Milligrams extractives per square inch=(*e*)/(*s*).
(*b*)*Heptane.* Milligrams extractives per square inch=*(e)/(s)(F)*
where:
e =Milligrams extractives per sample tested.
s =Surface area tested, in square inches.
F =Five, the ratio of the amount of extractives removed by heptane under exaggerated time-temperature test conditions compared to the amount extracted by a fat or oil under exaggerated conditions of thermal sterilization and use.
e '=Chloroform-soluble extractives residue.
ee '=Corrected chloroform-soluble extractives residue.
e' or*ee'* is substituted for*e* in the above equations when necessary.
If when calculated by the equations in paragraph (d)(5)(i) (*a*) and (*b*) of this section, the extractives in milligrams per square inch exceeds the limitations prescribed in paragraph (c) of this section, proceed to paragraph (d)(5)(ii) of this section (method for determining the amount of chloroform-soluble extractives residues).
(ii)*Chloroform-soluble extractives residue.* Add 50 milliliters of chloroform (freshly distilled reagent grade or a grade having an established consistently low blank) to the dried and weighed residue, (*e*), in the evaporating dish obtained in paragraph (d)(5)(i) of this section. Warm carefully, and filter through Whatman No. 41 filter paper (or equivalent) in a Pyrex (or equivalent) funnel, collecting the filtrate in a clean, tared evaporating dish (platinum or Pyrex). Repeat the chloroform extraction, washing the filter paper with this second portion of chloroform. Add this filtrate to the original filtrate and evaporate the total down to a few milliliters on a low-temperature hotplate. The last few milliliters should be evaporated in an oven maintained at approximately 221 deg.

F. Cool the evaporating dish in a desiccator for 30 minutes and weigh to the nearest 0.1 milligram to get the chloroform-soluble extractives residue (′). This′ is substituted for *e* in the equations in paragraph (d)(5)(i) (*a*) and (*b*) of this section. If the chloroform-soluble extractives in milligrams per square inch still exceeds the limitation prescribed in paragraph (c) of this section, proceed to paragraph (d)(5)(iii) of this section (method for determining corrected chloroform-soluble extractives residue).

(iii)*Corrected chloroform-soluble extractives residue* --(*a*)*Correction for zinc extractives.* Ash the residue in the evaporating dish by heating gently over a Meker-type burner to destroy organic matter and hold at red heat for about 1 minute. Cool in the air for 3 minutes, and place the evaporating dish in the desiccator for 30 minutes and weigh to the nearest 0.1 milligram. Analyze this ash for zinc by standard Association of Official Agricultural Chemists methods or equivalent. Calculate the zinc in the ash as zinc oleate, and subtract from the weight of chloroform-soluble extractives residue (′) to obtain the zinc-corrected chloroform-soluble extractives residue (*e′*). This*e′* is substituted for *e* in the equations in paragraph (d)(5)(i) (*a*) and (*b*) of this section.

(*b*)*Correction for wax, petrolatum, and mineral oil* --(*1*)*Apparatus.* Standard 10 millimeter inside diameter * 60 centimeter chromatographic column (or standard 50-milliliter buret with an inside diameter of 10-11 millimeters) with a stopcock of glass, perfluorocarbon resin, or equivalent material. The column (or buret) may be optionally equipped with an integral coarse, fritted glass disc and the top of the column (or buret) may be optionally fitted with a 100-millimeter solvent reservoir.

(*2*)*Preparation of column.* Place a snug pledget of fine glass wool in the bottom of the column (or buret) if the column (or buret) is not equipped with integral coarse, fritted glass disc. Overlay the glass wool pledget (or fritted glass disc) with a 15-20 millimeter deep layer of fine sand. Measure in a graduated cylinder 15 milliliters of chromatographic grade aluminum oxide (80-200 mesh) that has been tightly settled by tapping the cylinder. Transfer the aluminum oxide to the chromatographic tube, tapping the tube during and after the transfer so as to tightly settle the aluminum oxide. Overlay the layer of aluminum oxide with a 1.0-1.5 centimeter deep layer of anhydrous sodium sulfate and on top of this place an 8-10 millimeter thick plug of fine glass wool. Next carefully add about 25 milliliters of heptane to the column with stopcock open, and allow the heptane to pass through the column until the top level of the liquid just passes into the top glass wool plug in the column, and close stopcock.

(*3*)*Chromatographing of sample extract* --(*i*)*For chloroform residues weighing 0.5 gram or less.* To the dried and weighed chloroform-soluble extract residue in the evaporating dish, obtained in paragraph (d)(5)(ii) of this section, add 20 milliliters of heptane and stir. If necessary, heat carefully to dissolve the residue. Additional heptane not to exceed a total volume of 50 milliliters may be used if necessary to complete dissolving. Cool to room temperature. (If solution becomes cloudy, use the procedure in paragraph (d)(5)(iii)(*b*)(*3*)(*ii*) of this section to obtain an aliquot of heptane solution calculated to contain 0.1-0.5 gram of chloroform-soluble extract residue.) Transfer the clear liquid solution to the column (or buret). Rinse the dish with 10 millimeters of additional heptane and add to column. Allow the liquid to pass through the column into a clean, tared evaporating dish (platinum or Pyrex) at a dropwise rate of about 2 milliliters per minute until the liquid surface reaches the top glass wool plug; then close the stopcock temporarily. Rinse the Pyrex flask which contained the filtrate with an additional 10-15 milliliters of heptane and add to the column. Wash (elute) the column with more heptane collecting about 100 milliliters of total eluate including that already collected in the evaporating dish. Evaporate the combined eluate in the evaporating dish to dryness on a steam bath. Dry the residue for 15 minutes in an oven maintained at a temperature of approximately 221 deg. F. Cool the evaporating dish in a desiccator for 30 minutes and weigh the residue to the nearest 0.1 milligram. Subtract the weight of the residue from the weight of chloroform-soluble extractives residue (′) to obtain the wax-, petrolatum-, and mineral oil-corrected chloroform-soluble extractives residue (*e′*). This*e′* is substituted for *e* in the equations in paragraph (d)(5)(i) (*a*) and (*b*) of this section.

(*ii*) For chloroform residues weighing more than 0.5 gram. Redissolve the dried and weighed chloroform-soluble extract residue as described in paragraph (d)(5)(iii)(*b*)(*3*)(*i*) of this section using proportionately larger quantities of heptane. Transfer the heptane solution to an appropriate-sized volumetric flask (i.e., a 250-milliliter flask for about 2.5 grams of residue) and adjust to volume with additional heptane. Pipette out an aliquot (about 50 milliliters) calculated to contain 0.1-0.5 gram of the chloroform-soluble extract residue and analyze chromatographically as described in paragraph (d)(5)(iii)(*b*)(*3*)(*i*) of this section. In this case the weight of the dried residue from the heptane eluate must be multiplied by the dilution factor to obtain the weight of wax,

petrolatum, and mineral oil residue to be subtracted from the weight of chloroform-soluble extractives residue (′) to obtain the wax-, petrolatum-, and mineral oil-corrected chloroform-soluble extractives residue (*e′*). This*e′* is substituted for*e* in the equations in paragraph (d)(5)(i) (*a*) and (*b*) of this section. (Note: In the case of chloroform-soluble extracts which contain high melting waxes (melting point greater than 170 deg. F), it may be necessary to dilute the heptane solution further so that a 50-milliliter aliquot will contain only 0.1-0.2 gram of the chloroform-soluble extract residue.)
(e) Acrylonitrile copolymers identified in this section shall comply with the provisions of 180.22 of this chapter, except where the copolymers are restricted to use in contact with food only of the type identified in paragraph (c), table 1 under Category VIII.
[42 FR 14554, Mar. 15, 1977]

KNOW YOUR ENVIRONMENT. PROTECT YOUR HEALTH.

EWG analysis: Almost all new food chemicals greenlighted by industry, not the FDA

By Olivia Backhaus (EWG), **Melanie Benesh** (/news-insights/our-experts/melanie-benesh) (EWG)

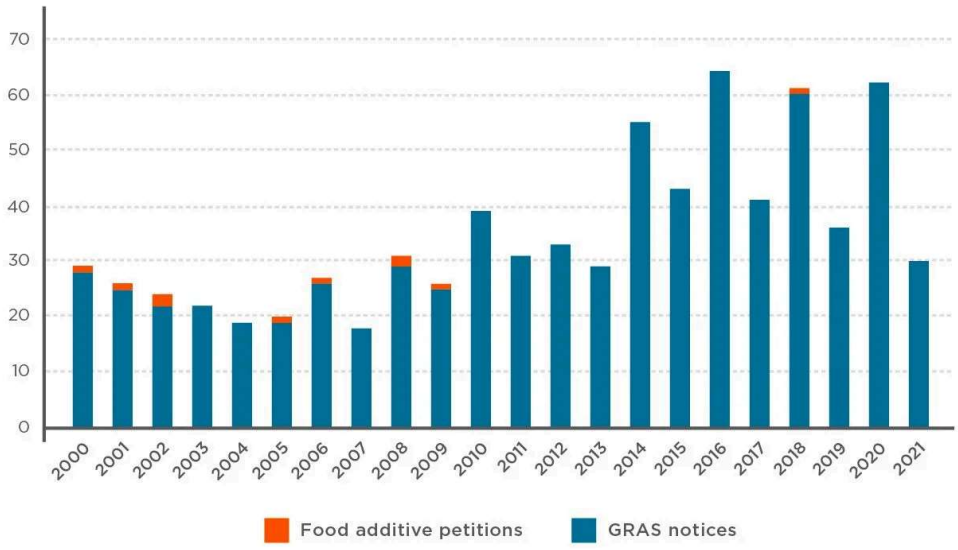
APRIL 13, 2022

Nearly 99 percent of all food chemicals introduced since 2000 were greenlighted for use by the food and chemical industry, according to a new EWG analysis – not by the Food and Drug Administration, the agency responsible for ensuring food is safe.

That's because food and chemical companies exploited a loophole in the law allowing them to decide which chemicals are safe to consume, contrary to what Congress intended when it enacted food chemical laws in 1958. What's more, taking advantage of this loophole is now the way most new chemicals, including **EGCG** (https://www.ewg.org/news-insights/news/2021/11/fda-not-food-companies-should-decide-whether-green-tea-extract-safe), **propyl paraben** (https://www.ewg.org/research/propyl-paraben) and **theobromine** (https://www.ewg.org/news-insights/news-release/2014/11/new-guide-warns-dirty-dozen-food-additives), are allowed in foods.

Since 2000, food and chemical companies have petitioned the FDA only 10 times to approve a new substance. By contrast, for 756 of 766 new food chemicals added to the food supply since then, or 98.7 percent, these companies have exploited a loophole for substances that are "**generally recognized as safe," or GRAS** (https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras#:~:text=%22GRAS%22%20is%20an%20acronym%20for,phrase%20Generally%20Recognized%20As%20Safe.). The loophole lets them – not the FDA – decide a substance is safe.

Food additive petitions versus GRAS notices for new chemicals (2000-2021)



Nine of the 10 food additive petitions for new chemicals were first filed more than 10 years ago, including:

- In 2000, Ecolab Inc. filed a petition for an **antimicrobial agent** (https://www.federalregister.gov/documents/2000/06/13/00-14906/ecolab-inc-filing-of-food-additive-petition).
- In 2001, Avecia, Inc. filed a petition for poly(hexamethylenebiguanide) hydrochloride (withdrawn).
- In 2002, Intralytix, Inc. filed a petition for an **antimicrobial agent** (https://www.federalregister.gov/documents/2002/07/22/02-18465/intralytix-inc-filing-of-food-additive-petition).
- In 2002, Safe Foods Corp. filed a petition for an **antimicrobial agent** (https://www.federalregister.gov/documents/2004/04/02/04-7399/secondary-direct-food-additives-permitted-in-food-for-human-consumption).
- In 2005, Kareem I. Batarseh filed a petition for an **antimicrobial agent.** (https://www.govinfo.gov/content/pkg/FR-2009-03-18/html/E9-5852.htm)
- In 2006, ARCH Chemicals, Inc. filed a petition for poly (iminoimidocarbonyliminoimido-carbonyliminohexamethylene) hydrochloride (withdrawn).
- In 2008, Lubrizol Advanced Materials, Inc. filed a petition for **cassia**

(awaiting approval).

- In 2008, Zentox Corp. filed a petition for monochloramine (withdrawn).
- In 2009, Ajinomoto Co. filed a petition for **advantame** (https://www.federalregister.gov/documents/2009/07/21/E9-17250/ajinomoto-co-inc-filing-of-food-additive-petition), a non-nutritive sweetener (an amended petition was filed in 2012).
- In 2018, Oakshire Naturals LP filed a petition for **vitamin D2 mushroom powder** (https://www.federalregister.gov/documents/2018/09/18/2018-20217/oakshire-naturals-lp-filing-of-food-additive-petition).

A food additive petition triggers rigorous pre-market safety review of a chemical, which can only be used after FDA approval. The 1958 Food Additives Amendment intended this review to be the primary way new food chemicals are approved.

But just one food additive petition for a new chemical has been filed in the past decade.

For the other 756 new food chemicals added to the food supply since 2000, food chemical companies exploited the GRAS loophole so they could make their own safety determinations.

This GRAS loophole was created in the 1958 law and intended to apply narrowly, to common ingredients like **sugar, vinegar and baking soda** (https://www.consumerreports.org/food-safety/gras-hidden-ingredients-in-your-food/). But as EWG's analysis shows, the loophole – not FDA safety review – has become the main way new chemicals are allowed into food.

When a company makes a **GRAS determination** (https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras#:~:text=%22GRAS%22%20is%20an%20acronym%20for,phrase%20Generally%20Recognized%20As%20Safe.), which shows the company believes "the substance is generally recognized,

the conditions of its intended use," it can **submit a notice** (https://www.fda.gov/food/generally-recognized-safe-gras/how-us-fdas-gras-notification-program-works) to the FDA, through a process that is entirely voluntary. The FDA can review these notices and issue a "no questions" letter, but it does not approve GRAS substances or affirm a company's GRAS determination.

If the FDA does raise questions about a company's safety conclusions, the company can **withdraw its GRAS notice** (https://www.cspinet.org/sites/default/files/attachment/GRAS-Infographic%20(1).pdf) – despite agency reservations – and continue to use the ingredient anyway, without further FDA review. Moreover, concerned citizens do not have the chance to provide public comment on or challenge GRAS determinations.

EWG's analysis includes only substances that have gone through this voluntary process, because little to no information is available when companies make their own GRAS determinations but do not notify the FDA. So the analysis is certainly an undercount of what is added to food through the GRAS loophole. Experts estimate **at least 1,000** (https://healthandenvironment.net/uploads-old/Published%20Navigating%20Article%2010.25.11.pdf) substances have been added to the food supply without GRAS notices being submitted to the FDA.

EWG also looked at filings related to new or modified uses for existing food chemicals, in addition to new chemicals. For new or modified uses of existing food chemicals, petitions were submitted slightly more often, at 42 times. But this number of petitions is dwarfed by the 195 GRAS notices submitted for new or modified uses of existing chemicals since 2000, in addition to the 756 new substances for which industry exploited the GRAS loophole.

The GRAS loophole puts consumers at risk

Because of the GRAS loophole, harmful ingredients have made their way into, and continue to enter, the food supply.

For example, the **Flavor and Extract Manufacturers Association** (https://www.consumerreports.org/food-safety/gras-hidden-ingredients-in-your-food/), or FEMA, a trade group composed of industry insiders, reviews and makes GRAS determinations on nearly all flavor ingredients. Seven **carcinogenic flavor** (https://www.ewg.org/news-insights/news-release/fda-bans-7-cancer-causing-food-additives-found-popular-foods) ingredients rubber-stamped as GRAS by

FEMA were later banned in response to a petition by EWG and other nonprofit groups in 2018.

Other GRAS substances include **BHA** (https://www.ewg.org/consumer-guides/ewgs-dirty-dozen-guide-food-additives#butylated-hydroxytoluene), classified as "reasonably anticipated to be a human carcinogen" by the National Toxicology Program, and **BHT** (https://www.ewg.org/consumer-guides/ewgs-dirty-dozen-guide-food-additives#butylated-hydroxytoluene), which may disrupt endocrine function by causing thyroid changes and affecting animal development. **Green tea extract EGCG** (https://www.ewg.org/news-insights/news/2021/11/fda-not-food-companies-should-decide-whether-green-tea-extract-safe), may increase risk of cancer but is classified as GRAS.

For decades, partially hydrogenated oils were considered GRAS – even though they are a major source of trans fat in the diet, which can increase cholesterol and harm the heart. When the **FDA revoked GRAS status** (https://www.fda.gov/food/food-additives-petitions/final-determination-regarding-partially-hydrogenated-oils-removing-trans-fat) in a rare action, in 2015, the agency said removing these oils from food "could prevent thousands of heart attacks and deaths each year."

Many of the GRAS notices lack critical health data. A 2020 **review** (http://blogs.edf.org/health/files/2020/09/Additives-Cumulative-Effects-Citizen-Petition-FINAL-9_23_20.pdf), of GRAS notices submitted since 1997 found they were nearly all inadequate. Among almost 900, only one assessed the effect of that chemical in combination with other similar chemicals, even though both manufacturers and the FDA are required to consider cumulative impacts as part of a safety determination.

It's time to close the GRAS loophole

The FDA is charged with protecting the U.S. food supply but has fallen short. Even Michael Taylor, a former **FDA deputy commissioner for food** (https://www.washingtonpost.com/national/food-additives-on-the-rise-as-fda-scrutiny-wanes/2014/08/17/828e9bf8-1cb2-11e4-ab7b-

696c295ddfd1_story.html), admitted in 2014 that the FDA "simply do[es] not have the information to vouch for the safety of many of these chemicals."

It is time to close the GRAS loophole and prevent new chemicals from being added to food through a side door, with no government oversight.

A bill introduced by Rep. Rosa DeLauro (D-Conn.), the **Toxic Free Food Act** (https://www.govtrack.us/congress/bills/117/hr3699/text), would require the FDA to narrow the loophole by making the GRAS process more transparent, with public input and robust data requirements.

And the **Food Chemical Reassessment Act of 2021** (https://www.congress.gov/117/bills/hr4694/BILLS-117hr4694ih.pdf), introduced by Rep. Jan Schakowsky (D-Ill.), aims to address inadequacies in food additive rules by requiring the FDA to regularly review and reassess food chemicals, many of which have not been reevaluated in decades.

Congress should act quickly to stop the continued use of unsafe chemicals in our food supply.

GRAS data analysis: Methodology

To compare uses of the GRAS loophole and petitions, EWG looked at how many of each were filed for new chemicals between 2000 to 2021.

To find out how often the loophole was used, EWG reviewed all filings in the FDA's GRAS **notice inventory** (https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices), since 2000. For new substance notices that were filed, we located and categorized all notices for duplicate substances, based on whether they were:

- the original filing for a new substance

Our analysis found that between 2000 and 2021, there were 756 original GRAS notices for novel food chemicals. And out of a total of 992 GRAS filings, there were 41 refilings and 195 filings for a new food chemical or varied use of an existing one.

Because submission of a GRAS notice is voluntary, it's impossible to know exactly how many more chemicals or uses companies have determined to be GRAS that are not included in this analysis.

To find out how many food additive petitions were filed, EWG searched the Federal Register for food additive petitions filed between 2000 and 2021. We identified a total of 97 petitions:

- 10 for new substances (one awaiting approval, three later withdrawn)
- 42 for a new or varied use of an already existing chemical (two later withdrawn)
- 11 to ban or restrict existing food chemicals (three have not been acted on by FDA, one denied, one withdrawn, and six granted)
- Nine for food irradiation (two later withdrawn)
- 12 correcting or amending previous petitions (*i.e.*, change scope of use, correct information error)
- Two converted to food contact notifications after the FDA created a new notification process for food contact chemicals
- One submitted in response to a determination that a substance is not GRAS
- 10 withdrawn and not refiled (original petitions included three petitions for new chemicals; two for food irradiation; two for a new or varied use of an already existing substance; and two converted to food contact notifications after the FDA recently launched a new process to regulate food additives that are food contact chemicals).

EWG's comparison focuses only on differences between GRAS notices and food additive petitions for new chemicals and requests to expand or change uses of existing chemicals added directly to food.

AREAS OF FOCUS: **Food & Water** (/areas-focus/food-water) **Water** (/areas-focus/food-water/water) **Children's Health** (/areas-focus/family-health/childrens-health) **Toxic Chemicals** (/areas-focus/toxic-chemicals) **Food Chemicals** (/areas-focus/toxic-chemicals/food-chemicals)

Disqus Comments

RELATED NEWS

Continue Reading

(/news-insights/news/2024/09/three-decades-later-bha-remains-food)

FOOD (/AREAS-FOCUS/FOOD-WATER/FOOD) FOOD CHEMICALS (/AREAS-FOCUS/TOXIC-CHEMICALS/FOOD-CHEMICALS)

Three decades later, BHA remains in food (/news-insights/news/2024/09/three-decades-later-bha-remains-food)

SEPTEMBER 19, 2024

In 1990, a doctor filed a petition asking the Food and Drug Administration to ban the use of the additive BHA in food – and they're still waiting for a response.

(/news-insights/news/2024/09/new-study-suggests-environmental-chemicals-can-trigger-early-puberty)

COSMETICS (/AREAS-FOCUS/PERSONAL-CARE-PRODUCTS/COSMETICS) CLEANING SUPPLIES (/AREAS-FOCUS/HOUSEHOLD-CONSUMER-PRODUCTS/CLEANING-SUPPLIES) REPRODUCTIVE HEALTH (/AREAS-FOCUS/FAMILY-HEALTH/REPRODUCTIVE-HEALTH) CHILDREN'S HEALTH (/AREAS-FOCUS/FAMILY-HEALTH/CHILDRENS-HEALTH)

New study suggests environmental chemicals can trigger early puberty in girls (/news-insights/news/2024/09/new-study-suggests-environmental-chemicals-can-trigger-early-puberty)

SEPTEMBER 13, 2024

A worrying trend of girls **starting puberty** (https://www.ewg.org/news-insights/news/2024/05/menstruation-starting-earlier-and-earlier-does-chemical-exposure-play) earlier is raising questions about whether chemical exposures play a role. Now **a new study suggests a link** (https://academic.oup.com/endo/article/165/10/bqae103/7749689?login=false) between certain chemicals in everyday products...

(/news-insights/news/2024/09/house-trio-urges-fda-end-foot-dragging-ban-toxic-formaldehyde-hair)

COSMETICS (/AREAS-FOCUS/PERSONAL-CARE-PRODUCTS/COSMETICS)

House trio urges FDA to end foot-dragging, ban toxic formaldehyde in hair straighteners (/news-insights/news/2024/09/house-trio-urges-fda-end-foot-dragging-ban-toxic-formaldehyde-hair)

SEPTEMBER 11, 2024

Three House lawmakers are calling out the Food and Drug Administration for its yearslong delay in banning hair-straightening treatments that contain or emit **cancer-causing** (https://pubmed.ncbi.nlm.nih.gov/31797377/) **formaldehyde** (https://www.ewg.org/skindeep/ingredients/702500-FORMALDEHYDE/). They urge the...

(/news-insights/news/2024/09/what-are-parts-million-billion-and-trillion)

PFAS CHEMICALS (/AREAS-FOCUS/TOXIC-CHEMICALS/PFAS-CHEMICALS)

What are parts per million, billion and trillion? (/news-insights/news/2024/09/what-are-parts-million-billion-and-trillion)

SEPTEMBER 6, 2024

EWG often talks about pollution and health risks in terms of parts per billion or trillion. But what does that mean in simple terms? How can you use this information to live a healthier life?

ALL NEWS (/NEWS-INSIGHTS/NEWS)