A. Wallace Hayes

Comments on "Draft Regulatory Determinations Report to the Legislature Draft Regulatory Determinations Report to the Legislature"

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I have a doctorate and postdoctoral training in toxicology. I am certified in toxicology by the American Board of Toxicology and the Federation of European Toxicologists and European Societies of Toxicology. I am a fellow of the Academy of Toxicological Sciences and the American Association for the Advancement of Science. I have 40 years of experience with more than 350 peered review publications. I have worked both in industry and academy, examining the safety of chemicals primarily used in products that consumers, including children, encounter. In addition to understanding the hazard or toxicity of chemicals and their potency, my experience and expertise include exposure assessment, a critical element for understanding and projecting risk.

The "Draft Regulatory Determinations Report to the Legislature Draft Regulatory Determinations Report to the Legislature" deals with a complex topic. Our ultimate goal is to protect human health and the environment.

My comment concern two topics:

- Hazard versus risk
- Grouping of chemicals

Hazard Versus Risk*

To understand hazard, we must first understand four basic principles of toxicology—dose matters, timing is critical, people differ and things change. A good example of dose matters comes from the world of vitamins. Most fat-soluble vitamins have both recommended intakes as well as tolerable upper intake levels. An adequate intake of vitamin A is essential for vision, cell differentiation, membrane structure and function, reproduction, immune system functions, and organ development during embryonic and fetal growth. However, there is the potential for harmful effects of long-term overdoses of preformed vitamin A, including liver damage. Although adequate intake of vitamin A is necessary for normal fetal development, excessive intake of vitamin A (retinol) during the first 3 months of pregnancy can cause birth defects. For this reason, the Institute of Medicine recommends a UL for vitamin A of 10,000 IU per day in adults.

The concept of "timing is critical" can be demonstrated by the example of thalidomide, a drug once approved in Europe for nausea and to alleviate morning sickness in pregnant women. Shortly after the drug began selling in Germany, between 5,000 and 7,000 infants were born with phocomelia

(malformation of the limbs). It was recognized that the timing of exposure was as important as the dose for teratogenic effects. Today, thalidomide is used to treat people for several conditions. Therefore, when used outside this critical period of human development, thalidomide does not produce the adverse effects that were so tragically manifested during its use as a morning sickness therapy.

The fact that people differ is reflected in our genetic makeup as polymorphisms or very small changes in our DNA that cause our bodies to respond differently to certain chemicals. For example, in the case of the artificial sweetener aspartame, a warning label is required: "Phenylketonurics [PKU]: contains phenylalanine." PKU occurs in approximately 1 in 10,000 babies born in the US, resulting in the body's inability to break down the essential amino acid phenylalanine, leading to toxic levels of this amino acid. People without this polymorphism can safely consume and enjoy aspartame-sweetened beverages and foods.

The fourth basic principle, things change, is based on how exogenous chemicals are metabolized. An example is the food-drug interaction that occurs with grapefruit. Grapefruit juice increases the absorption of certain drugs into the bloodstream and decreases excretion. For example, if you drink a lot of grapefruit juice while taking certain statin drugs, too much of the drug may stay in your body, increasing your risk for liver damage and muscle breakdown that can lead to kidney failure.

At this point, we have looked at four factors that affect the potential for a hazard to be expressed. Risk, however, is equal to hazard times exposure, which can be remembered by the simple acronym RITE (Risk Is Toxicity × Exposure). Bluntly, no exposure, no risk! Although there is no plausible hazard from exposure to thimerosal from vaccines, despite a Lancet report to the contrary (paper retracted), it's comforting to know that thimerosal, used to prevent bacterial growth with repeated entry into a vial, was never used in the MMR vaccine or vaccines for chickenpox or polio in the United States, because in the U.S., these were single-use products. Even with exposure, the amount of exposure is critical. An example is found in our favorite morning beverage. Coffee is chemistry in a cup! It contains more than 1,000 aroma compounds, including caffeine and a spectrum of potential carcinogens. The health controversies surrounding coffee have been the focus of numerous studies addressing a long list of animal toxicities and human disease outcomes. Acrylamide, a product of roasting, is found in an array of food products, including coffee, and fried, baked, or toasted goods. According to the U.S. National Toxicology Program and the International Agency for Research on Cancer, there is clear evidence that acrylamide is an animal carcinogen. A typical coffee drinker's exposure to acrylamide of about 4–6 μg/day is equivalent to that detected in three to five cups of java. Despite these potential adverse health effects, many negative health myths about coffee drinking may now be transformed into validated health benefits due to more recent mechanistic and epidemiologic research studies. For example, the consumption of five or more cups of coffee daily is associated with improved glucose tolerance and reduced risk of type 2 diabetes, cardiovascular disease, and some forms of cancer. Even in cases of toxic or carcinogenic chemicals, dose matters!

Grouping of chemicals

"This conclusion is consistent with opinions expressed by the scientific community in the San Antonio Statement on Brominated and Chlorinated Flame Retardants, which was signed by over 200 scientists from 30 countries with expertise on human health, the environment, and fire safety (Birnbaum & Bergman, 2010). The statement summarizes concerns from scientific experts on the

persistent, bioaccumulative, and toxic properties of chlorinated and brominated flame retardants, their use, and resulting exposure in humans and wildlife."

This statement is largely based on an older class of flame retardants, the PBDEs, which have been replaced by better alternatives that do not share these properties.

Most significant are the findings of the 2019 National Academies of Sciences (NAS) consensus report on the grouping of flame retardants.

"The committee used cheminformatic approaches to create OFR subclasses. A public set of chemotypes and methods that have been developed by Yang et al. (2015) and Richard et al.(2016) were used to identify the chemotypes present in the seed chemicals, which are listed in Figure 3-1. Using the chemotypes, the committee was able to identify several generic classes that represented the entirety of the OFR seed set (Table 3-1). Merging the biology-informed groups with the chemotypes listed in Figure 3-1 led to the formulation of 14 OFR categories for the inventory of 161 OFR chemicals (Table 3-2). Appendix B provides additional details on how the subclasses were formed and evaluated. The committee recommends that CPSC use the subclasses in Table 3-2 at least as a starting point for the class-based hazard assessment of OFRs."

As you resolve your position document, I urge you to carefully reconsider your decision to assess essentially all OFRs as being unacceptable based on the current literature and especially the NAS consensus report on the grouping of flame retardants.

Thank you for the opportunity to comment.

Comments are submitted in my individual capacity. I serve as a paid consultant to the North American Flame Retardant Alliance (NAFRA) as a member of its Science Advisory Council.

Submit via https://hwtr.ecology.commentinput.com/?id=HWQc5

* Hayes, A. Wallace, C.L. Kruger, and R.A. Clemens. 2015. Understanding the Difference. Food Safety Magazine December 2015 pp. 15-17.