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Item reviewed

Product – Chemical Profile for Treatments Containing Perfluoroalkyl or Polyfluoroalkyl Substances for Use on Converted Textiles or Leathers

CalEPA Scientific Review Program

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence. I am reviewing ***Conclusion 2*****: Exposure to any PFASs found in treatments intended for use on converted textiles or leathers or to their degradation products, during product manufacturing, use, or at its end-of-life, may contribute to or cause significant or widespread adverse impacts to humans or biota.**

Brief summary of approach to external peer-review by the peer-reviewer

In addition to the specific issues presented in ***Conclusion 2***, I also will be addressing the following questions:

(a) In reading the product-chemical profile, are there any additional scientific issues that are part of the scientific basis of the proposed regulation not described above? If so, please comment.
(b) Taken as a whole, is the scientific portion of the proposed regulation based upon sound scientific knowledge, methods, and practices?

In reading the product-specific profile (the "Product), there did not appear to be any additional scientific issues that were part of the scientific basis of the proposed regulation that were not described in the Product or in ***Conclusion 2***.

The scientific portion of the proposed regulation appears to be based upon sound scientific knowledge, methods, and practices. Two areas of ***Conclusion 2***, points #4 and #8, may require additions and/or clarifications. Point #4 could include additional toxicological hazard traits for long-chain PFASs and point #8 appeared to be weakly supported by sound scientific knowledge. However, as noted in the charge to external peer-reviewers, "some proposed regulatory actions might rely significantly on professional judgment where available scientific data are not as extensive as desired to support the statutory requirement for absolute scientific rigor. In these situations, the proposed course of action is favored over no action." Thus, the proposed course of action, as put forward in point #7 under ***Conclusion 2***, is preferable over no action.

Each point, below, reflects the application of these questions to each of the nine specific points listed under ***Conclusion 2***. References cited also are included to support my external peer-review. Throughout my peer review, I will refer to the "Product – Chemical Profile for Treatments Containing Perfluoroalkyl or Polyfluoroalkyl Substances for Use on Converted Textiles or Leathers" as the "Product."

Conclusion 2-specific points addressed by the peer-reviewer

(1) All PFASs have at least one hazard trait according to the Safer Consumer Products regulations. At a very minimum, PFASs are either extremely persistent (e.g., PFAAs), or are PFAA precursors and hence have extremely persistent degradation products.

One reason for the use of PFASs in commercial products and industrial applications is the strength of the carbon-fluorine bond. According to Buck et al. (2011; cited in the Product): "The C–F bond is extremely strong and stable (Smart 1994). The chemical and thermal stability of a perfluoroalkyl moiety, in addition to its hydrophobic and lipophobic nature, lead to highly useful and **enduring** properties in surfactants and polymers into which the perfluoroalkyl moiety is incorporated (Kissa 1994, 2001)" [emphasis added]. This same manuscript (Buck et al., 2011; cited in the Product) notes that "PFAAs are important both because they are highly persistent substances that have been directly emitted to the environment or are formed indirectly from the environmental degradation or metabolism of precursor substances…" This manuscript reflects scientific knowledge across a range of sectors (as represented by listed affiliations of the co-authors) that PFASs are persistent, that this persistence is directly related to their physical-chemical structure and intended functionality, and that PFAA precursors degrade to persistent degradation products. Therefore, the Product's conclusion that all PFASs have at least one hazard trait and at a very minimum, are either extremely persistent or are PFAA precursors and hence have extremely persistent degradation products is based on sound scientific knowledge.

(2) Longer-chain PFAAs such as perfluorooctanoic acid (PFOA) and perfluorosulfonic acid (PFOS) tend to bioaccumulate. These longer-chain PFAAs have been voluntarily phased out by most manufacturers and are restricted (but not banned) in treatments for converted textiles or leathers by US EPA's significant new use rule (SNUR).

The conclusion that longer-chain PFASs can bioaccumulate in living organisms is based on scientific knowledge demonstrating that PFASs are bioavailable to living organisms from environmental media (i.e., air, water, soil, food) and can become concentrated inside living organisms relative to levels in the environment. Support for bioaccumulation comes from published bioconcentration, bioaccumulation, and/or biomagnification factors that identify values for longer-chain PFASs that meet or exceed criteria for these values outlined in applicable California code. In addition, scientific studies have demonstrated that longer-chain PFASs can be conveyed from a mother to her offspring, including in humans, through placental and lactational transfer. Numerous studies included in the Product report that PFASs can accumulate in the placenta and transfer to the developing fetus as the fetus grows throughout gestation and other studies listed in the Product also report PFASs in blood of umbilical cords, further supporting the transfer of PFASs from mother to offspring and thus bioaccumulation in those offspring. When the persistence of PFASs also is considered in that PFASs in environmental media lead to continuous internal exposures in living organisms, traditional measures of bioaccumulation may underestimate PFASs accumulation into living organisms,

including developing organisms exposed via the mother. Therefore, the Product's conclusion is based on scientific knowledge that PFASs can move from many types of environmental media, including air, water soil, and food, into living organisms, leading to internal levels in living organisms that may exceed concentrations in any one environmental medium. Therefore, the Product's conclusion that longer-chain PFAAs such as PFOA and PFOS tend to bioaccumulate is based on sound scientific knowledge.

(3) Shorter-chain PFAAs such as perfluorohexanoic acid (PFHxA), appear not to bioaccumulate in humans and animals, but bioaccumulate in plants and are very mobile in environmental media, which is another exposure potential hazard trait of concern under the Safer Consumer Product regulations.

Accumulating scientific knowledge for shorter-chain PFASs demonstrate that they can be detected in plants at concentrations higher than environmental levels and that accumulation may differ depending on plant type, plant part, or soil amendment in which the plant is grown (Ghisi et al., 2019). Existing evidence associated with shorter-chain PFAAs indicates that while they are bioavailable to humans and animals, they appear to be more rapidly excreted from these organisms compared to longer-chain PFASs. Thus, a feature of shorter-chain PFASs is that they have shorter half-lives in humans and animals. However, two additional concerns are associated with hazard traits of concern for shorter-chain PFASs. One is that shorter-chain PFASs have increased mobility in the environment compared to longer-chain PFASs, potentially leading to a greater breadth of environmental contamination that may lead to more widespread human exposures. Therefore, the Product's conclusion that shorter-chain PFASs possesses an exposure potential hazard trait of concern (mobility), is consistent with the scientific knowledge concerning shorter-chain PFASs. Another concern associated with shorter-chain PFASs is due to their persistence, which will lead to continuous exposures in living organisms. This continuous exposure may exceed the rate at which they are eliminated from the body, potentially leading to bioaccumulation. This is addressed under (1), above, for all PFASs, but it may be worth mentioning in the Product that when persistence is combined with mobility the hazard trait is enhanced.

(4) The toxicological hazard traits of longer-chain PFAAs, which may still be present in imported treatment products, have been well established in animal and human epidemiologic studies. In humans, these include:

- carcinogenicity (kidney and testicular cancers);
- cardiovascular toxicity (increased serum cholesterol);
- endocrine toxicity (thyroid disease);
- immunotoxicity (immune dysregulation); and
- reproductive toxicity (pregnancy-induced hypertension).

The toxicological hazard traits of longer-chain PFAAs listed above are mostly applicable to PFOA and PFOS but a few other longer-chain PFASs are included in

assessments of effects of PFASs on experimental animal models and humans. Additional toxicological hazard traits that have been associated with PFAS-exposed humans are discussed in the Toxicological Profile for Perfluoroalkyls by the Agency for Toxic Substances and Disease Registry (ATSDR, 2018; cited in the Product). The ATSDR report lists, in addition to those above, that effects on the liver and effects on development have also been associated with exposure to PFASs in studies of humans as well as studies of experimental animal models. Therefore, the Product's conclusion that hazard traits of longer-chain PFAAs have been well established in humans with respect to exposed humans is based on sound scientific knowledge but should be extended to include effects on the liver and effects on development, which also are based on sound scientific knowledge.

(5) The toxicological hazard traits of the shorter-chain PFAAs are still emerging, based on more recent rodent, zebrafish, in vitro, and toxicokinetic modeling studies. These include:

- o developmental toxicity (observed in zebrafish);
- o endocrine toxicity (PPAR-alpha activation in vitro);
- o hematotoxicity (reduced red blood cell count, hemoglobin, and hematocrit in rodents);
- o hepatotoxicity (increased liver weight, based on toxicokinetic modeling);
- o neurodevelopmental toxicity (suppression of neuronal differentiation in vitro);
- o ocular toxicity (delayed pupil response in rodents); and
- o reproductive and developmental toxicity (fetal resorption and delayed eye opening in rodents).

The Product notes that the database for the toxicological hazard traits of the shorter-chain PFASs is still emerging, however, recent data across a span of experimental animal models as well as data from in vitro and toxicokinetic modeling support the listed hazard traits. Recently, the U.S. Environmental Protection Agency (EPA) released draft toxicity assessments for a perfluoroether acid (PFEA) known by the trade name GenX and a shorter-chain PFAA (perfluorobutanesulfonic acid or PFBS) due to their use in myriad consumer products and presence in environmental media. In their draft toxicity assessments, the U.S. EPA developed draft chronic toxicity values for GenX based on findings of liver toxicity in animal studies and for PFBS based on findings of kidney and thyroid toxicity in animal studies (U.S. EPA, 2018a,b). Additionally, several U.S. states have developed toxicity values for shorter-chain PFAS, including Michigan, Minnesota, and North Carolina, demonstrating that public health concerns exist for these shorter-chain PFAS. Therefore, the Product's conclusion that while the database for the toxicological hazards of shorter-chain PFAAs are still emerging, some toxicological hazards traits have been identified and these are based on sound scientific knowledge.

(6) Recent studies show that the intermediate degradation products of shorter-chain fluorotelomer-based PFASs, like the ones used in treatments for converted textiles and leathers, are more bioaccumulative and toxic than PFHxA, raising concerns for potential adverse impacts.

PFHxA is an environmental and biological degradation product of 6:2 fluorotelomer alcohol (6:2 FTOH), which is a shorter-chain PFAS used as a starting substance in the development of certain PFAS used in treatments for converted textiles and leathers (as well as food packaging). PFHxA has been used as a surrogate for 6:2 FTOH toxicity in several published studies evaluating chronic toxicity and carcinogenicity, reproductive and developmental toxicity, and bioaccumulation. However, recent studies, most notably one by Rice et al. (2020; cited in the Product), demonstrated that 6:2 FTOH is more toxic compared to PFHxA and that its intermediate metabolites (5:3 FT carboxylic acid and perfluoroheptanoic acid or PFHpA) are eliminated from experimental animal models more slowly compared to PFHxA. The authors of this study suggested that their findings mean that human health risks to 6:2 FTOH may be underestimated by relying on studies of PFHxA (Rice et al., 2020). These recent data highlight the importance of evaluating the toxicity of parent compounds, their intermediate degradation products, and final degradation products. Therefore, the Product's conclusion that intermediate degradation products of shorter-chain fluorotelomer-based PFASs, such as those used in treatments for converted textiles and leathers, is based on sound scientific knowledge as well as emerging methods and practices for evaluating PFAS toxicity across a lifecycle.

(7) PFAAs display environmental hazard traits: phytotoxicity and wildlife developmental, reproductive, or survival impairment.

Accumulating scientific evidence for PFASs demonstrate that in laboratory studies of environmentally relevant species of algae, aquatic plants, terrestrial plants, fish, amphibians, avian species, and important pollinating insects and in birds exposed in the wild, death and/or developmental, reproductive, and/or survival impairment occur. Some data also exist to support that shorter-chain PFASs and PFAA precursors can induce similar effects. While the database on hazard traits in free-living aquatic and terrestrial wildlife species is still emerging, the existing database indicates that PFAAs are detectable in blood and/or tissues of such organisms. However, a gap still exists in our understanding of how exposure to PFASs may affect free-living organisms. The Interstate Technology Regulatory Council (ITRC) updated their summary of the ecotoxicological effects of PFASs in April of 2020 (ITRC, 2020) and noted that while studies in aquatic and terrestrial invertebrates demonstrate hazard traits (survival impairment or effects of reproduction and/or development) studies in aquatic and terrestrial vertebrates still are limited in number. Therefore, although the database for free-living species exposed to PFASs "in the wild" are limited in number, laboratory studies of environmentally relevant species indicate hazard traits associated with PFAS exposure, which supports the conclusion in the Product and is based on sound scientific knowledge.

(8) PFAAs may have cumulative impacts with one another and with other hazardous chemicals. Some studies found that other PFAAs can cause adverse impacts

when mixed with other toxicants, even at doses at which the individual PFAAs and the other toxicants produced no observed adverse impacts.

Living organisms are exposed to mixtures of PFAAs, PFASs, and other chemical compounds that produce toxicological hazard traits and this is acknowledged in the Product. However, studies of PFAA and/or PFAS mixtures or of PFASs and/or PFASs mixed with other chemical compounds are limited, which is acknowledged in the Product. The Product presents findings from six different published studies of PFASs mixed with other chemical compounds, including polychlorinated biphenyls (PCBs), a variety of endocrine disrupting chemicals (including those associated with pharmaceutical and personal care product pollutants), heavy metals, pesticides, and nanoparticles. The results of these studies are equivocal for several reasons. First, two of the studies were in cells/cell lines and it is unclear if the outcomes are tied to adverse phenotypes. Second, three of the studies were in zebrafish or juvenile salmon and the outcomes were either perturbations to specific cellular functions or gene expression and it is unclear if these perturbations were associated with adverse phenotypes. Finally, the one mixture study in rats produced no or weak effects. However, this is not the case when mixtures of PFASs are considered. The drinking water health advisory for PFOA and PFOS set by the U.S. EPA (U.S. EPA, 2020; cited in the Product) is based on their cumulative concentration and at least four individual U.S. states have drinking water health advisories the consider the cumulative concentrations of 5-6 individual PFASs (Cousins et al., 2020). Therefore, the Product's conclusion that PFAAs may have cumulative impacts with one another is based on sound scientific knowledge, methods, and practices.

(9) The adverse impacts associated with PFAAs are relevant to the entire class of PFASs because other PFASs either:

- degrade to PFAAs in humans, biota, or the environment (i.e., are PFAA precursors);
- form PFAAs during combustion; or
- are manufactured using PFAAs and contain them as impurities.

The conclusion that adverse impacts associated with PFAAs are relevant to the entire class of PFASs because other PFASs degrade to PFAAs, form PFAAs during combustion, or are manufactured using PFAAs and contain them as impurities is based on sound scientific knowledge reporting detectable levels of PFAAs in degradation or combustion studies as well as knowledge of manufacturing processes involving PFASs. While certain PFASs, such as fluoropolymers, do not degrade in the same was as non-polymer PFASs, such as through environmental or metabolic degradation of precursor compounds, they can release PFAAs during production and produce PFAAs at product end-of-life disposal/destruction, such as through combustion. Grouping PFASs as sub-groups within the class or even grouping them all together in one class is an approach being implemented or considered across the globe (Cousins et al., 2020). Therefore, the Product's conclusion that PFAAs can arise from a wide variety of

PFASs and as PFAAs possess environmental hazard traits, PFASs themselves, through processes that lead to PFAAs, also possess environmental hazard traits, is based on sound scientific knowledge, methods, and practices.

References (references cited in the Product are not listed here)

Cousins IT, et al. 2020. Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health. *Environmental Science Processes & Impacts*. DOI: 10.1039/d0em00147c.

Ghisi R, Vamerali T, Manzetti S. 2019. Accumulation of perfuorinated alkyl substances (PFAS) in agricultural plants: A review. *Environmental Research*. 169:326-341.

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U.S. EPA. 2018a. Toxicity assessment: Human health toxicity values for hexafluoropropylene oxide (HPFO) dimer acid and its ammonium salt (CASRN 13252-13-6 and CASRN 62037-80-3). https://www.epa.gov/sites/production/files/2018-11/documents/genx_public_comment_draft_toxicity_assessment_nov2018-508.pdf.

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