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Item reviewed

Product – Chemical Profile for Food Packaging Containing Perfluoroalkyl or Polyfluoroalkyl Substances

CalEPA Scientific Review Program

Based on my expertise and experience, I am reviewing the assumptions, findings or conclusions I agreed I could review with confidence. I am reviewing ***Conclusion 2*****: Exposure to any PFASs found in plant fiber-based food packaging products, 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) Are there any scientific subjects that are part of the scientific basis of the proposal that are not described in the proposal or ***Conclusion 2***?
(b) Taken as a whole, is the proposal based upon sound scientific knowledge, methods, and practices?

In reading the proposal (the "Product"), there did not appear to be scientific subjects that were part of the scientific basis of the proposed regulation that were not described in the Product or in ***Conclusion 2***.

Taken as a whole, the proposal (the "Product") appears to be based upon current and sound scientific knowledge, methods, and practices. No areas of the Product or ***Conclusion 2*** were identified as needing additions and/or clarifications.

Each point, below, reflects the application of these questions to each of the seven specific points listed under ***Conclusion 2***. References cited also are included to support the external peer-review. Throughout the peer review, I will refer to the "Product – Chemical Profile for Food Packaging Containing Perfluoroalkyl or Polyfluoroalkyl Substances " 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 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…” The Buck et al. (2011) 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 end products. Another manuscript cited in the Product is by Cousins et al. (2019), which asserts that “it will take decades, centuries, or even longer to reverse contamination and therefore effects” of exposure to highly persistent chemicals, including PFASs. A recent publication by Cousins et al. (2020, listed below and not included in the Product likely due to the date of publication) applies this “P-sufficient approach” directly to PFASs and emphasizes that once adverse effects are identified for PFASs, both exposure and associated adverse effects will not be easily reversible. The manuscripts by Cousins et al. (2019 and 2020) include co-authors, like the Buck et al. (2011) publication, from a range of sectors. The Product also notes that while PFAAs may reflect a small subset (approximately 1%) of all PFASs, “they are terminal degradation products, manufacturing aids/feedstocks, or impurities of other PFAS class members, which makes their hazard traits relevant to the entire class.” Therefore, the Product’s conclusion that all PFASs have at least one hazard trait and at a very minimum, are either extremely persistent or have extremely persistent degradation products is based on current and sound scientific knowledge.

Cousins et al. 2020b. The high persistence of PFAS is sufficient for their management as a chemical class. Environmental Science Processes & Impacts. 22:2307-2312.

(2) *The U.S. Food and Drug Administration (FDA) prohibits the use of certain longer-chain PFASs in food-contact materials because of their potential to cause adverse human health impacts. These effects, which are well established in animal and human studies, include kidney and testicular cancers, thyroid disease, reduced immune response, and pregnancy-induced hypertension. However, evidence from*

animal, in vitro, and modeling studies also links the degradation products of FDA-approved PFASs with multiple toxicological hazard traits, including developmental toxicity, endocrine toxicity, hepatotoxicity, neurodevelopmental toxicity, and reproductive and developmental toxicity.

The toxicological hazard traits of longer-chain PFASs, including kidney and testicular cancers, thyroid disease, reduced immune response, and pregnancy-induced hypertension are mostly applicable to two specific PFAAs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). However, a handful of other longer-chain PFASs have been included in assessments of health effects of PFASs in exposed experimental animal models and humans. These additional longer-chain PFASs have been discussed in detail in the Toxicological Profile for Perfluoroalkyls by the Agency for Toxic Substances and Disease Registry (ATSDR, 2018; cited in the Product) as well as a recent publication by Fenton et al. (2020, listed below and not included in the Product, likely due to the date of publication). The ATSDR Profile and the publication by Fenton et al. (2020) note additional toxicological hazard traits, including developmental toxicity, endocrine toxicity, hepatotoxicity, neurodevelopmental toxicity, and reproductive toxicity, associated with a wider range of longer-chain PFASs (i.e., beyond PFOA and PFOS) and degradation products of longer-chain PFASs not contained in the ATSDR Profile. Research associated with degradation products of PFAAs is ongoing, which the Product noted, and toxicities have been described for degradation products/impurities. Additionally, as noted in the Product, while PFAAs may reflect a small subset (approximately 1%) of all PFASs, "they are terminal degradation products, manufacturing aids/feedstocks, or impurities of other PFAS class members, which makes their hazard traits relevant to the entire class." Therefore, the Product's conclusion that longer-chain PFASs used in food-contact materials and degradation products of FDA-approved PFASs have the potential to cause adverse human health impacts is based on current and sound scientific knowledge.

Fenton et al. 2020. Per- and polyfluoroalkyl substance toxicity and human health review: Current state of knowledge and strategies for informing future research. Environmental Toxicology and Chemistry. https://doi.org/10.1002/etc.4890.

(3) Shorter-chain PFAAs such as perfluorohexanoic acid (PFHxA), appear not to bioaccumulate in humans and animals, but bioaccumulate in plants, including those grown for agriculture, 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; cited in the Product). 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 and have a lower bioaccumulation potential than 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 stated explicitly in the Product and the other is implied. One concern is that shorter-chain PFASs have high mobility in the environment, potentially leading to a greater breadth of environmental contamination that may lead to more widespread exposures to living organisms. Therefore, the Product's conclusion that shorter-chain PFASs possesses an exposure potential hazard trait of concern (mobility), is consistent with current and sound scientific knowledge concerning shorter-chain PFASs. Another concern associated with shorter-chain PFASs is their persistence, which will lead to continuous and long-term exposures to living organisms. This also is acknowledged in the Product, but data on bioaccumulation and biomagnification of shorter-chain PFASs, other than PFAAs, has not been evaluated. Therefore, the Product's conclusion that shorter-chain PFASs are very mobile in environmental media, which is another exposure potential hazard trait of concern under the Safer Consumer Product regulations, is based on current and sound scientific knowledge

(4) Recent studies show that the intermediate degradation products of the shorter-chain fluorotelomer-based PFASs currently used widely in plant fiber-based food packaging are more bioaccumulative and toxic than PFHxA, raising concerns for potential adverse impacts. As a result, FDA negotiated a three-year voluntary phase out with some of the manufacturers beginning January 1, 2021. However, as the history of regrettable substitutions illustrates, the PFASs that will continue to remain in use may not necessarily be safer, but just less well studied.

PFHxA, a shorter-chain PFAS that is one degradation product of 6:2 FTOH chemistries (6:2 FTOH is 6:2 fluorotelomer alcohol, a shorter-chain PFAS used in some fast food packaging) has been studied with respect to chronic toxicity, carcinogenicity, and reproductive and developmental toxicity, and has been found to be less toxicologically potent than longer-chain PFASs. These studies of PFHxA as a degradation product of 6:2 FTOH has led to an assumption that 6:2 FTOH is a less toxic substitution for the longer-chain PFASs. However, degradation of 6:2 FTOH also results in another shorter-chain PFAS, 5:3 fluorotelomer carboxylic acid. Studies by Kabadi et al. (2020) and Rice et al. (2020), cited in the Product, demonstrate bioaccumulation and toxicity potential of 6:2 FTOH, likely from this other degradation product, as *higher* than PFHxA. These studies highlight that using data from studies of PFHxA may underestimate the potential bioaccumulation and toxicity of 6:2 FTOH. These studies also highlight that parent compounds and all degradation products need to be part of safety assessments. Therefore, the Product's conclusion that PFASs in use may not necessarily be safer than the PFASs they intended to replace is consistent with current and sound scientific knowledge concerning emerging data on substitutes and lack of data on substitutes.

(5) *PFAAs also 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 continues to grow, evidence from existing studies indicates that PFAAs are detectable in blood and/or tissues of such free-living aquatic and terrestrial wildlife as well as in the tissues of plants. 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 September 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 to a small number of studies and a small number of individual PFASs. The ITRC also noted that few to no studies are available in avian or mammalian wildlife or plants and that this represents a significant data gap with respect to the effects of PFAS exposure on ecological communities (ITRC, 2020). Therefore, although the database for free-living species exposed to PFASs “in the wild” are limited in number and limited to a small number of individual PFASs, laboratory studies of environmentally relevant species indicate hazard traits associated with PFAS exposure, which supports the conclusion in the Product and is based on current and sound scientific knowledge regarding ecotoxicity of PFASs.

(6) *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 also is acknowledged in the Product. The Product cites an approach developed by RIVM (a Dutch agency that has similarities to the U.S. FDA and U.S. EPA) that uses a “relative potency factor (RPF)” method to compare mixtures of PFASs to PFOA to determine how much more or less toxic a PFAS mixture is compared to PFOA alone. The Product also notes that RPFs have only been calculated for 20 individual PFASs and that they rely heavily on subacute and subchronic studies where the PFASs were delivered orally to rodents. Apart from this method, there do not yet appear to be well-developed methods for evaluating cumulative impacts of PFASs with one another. Regardless aggregate toxicity of PFASs has been incorporated into drinking water advisories and regulations in the U.S. and beyond.

The drinking water health advisory for PFOA and PFOS set by the U.S. EPA (cited in the Product) is based on their cumulative concentration. Several individual U.S. states have drinking water health advisories that consider cumulative concentrations of 5-6 individual PFASs as do several European Union member countries (Cousins et al., 2020a; not cited in the Product). The European Commission also has issued a directive that will set limits based on all PFASs in drinking water (Council of the European Union, 2020a,b; cited in the Product). Therefore, the Product's conclusion that PFAAs may have aggregate impacts with one another is based on current and sound scientific knowledge, methods, and practices.

With respect to mixtures of PFASs with other hazardous agents, 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 can be phenotypically anchored to adverse health outcomes in whole organisms (i.e., are these changes observed in cells/cell lines likely to produce adverse health outcomes in exposed rodent models or humans?). 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 (i.e., negative health effects in the exposed organisms). Finally, the one mixture study in rats exposed to a mixture of PFHxS and 12 endocrine-disrupting compounds produced no or weak effects. Each of the limitations listed here, however, are acknowledged in the Product and the Product highlights a 2017 National Academies of Science (NAS) report that suggests certain combinations of PFASs or co-exposure to certain PFASs and other chemicals has the potential to contribute to disease by altering biological pathways or mechanisms. The Product acknowledges that more scientific research is required to verify the effects of mixtures of PFASs and mixtures of PFASs and other hazardous agents. Therefore, the conclusion that PFASs may have cumulative impacts with other hazardous agents is based and current and sound scientific knowledge.

Cousins et al. 2020a. Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health. Environmental Science Processes & Impacts. 22:1444-1460.

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

- o *degrade to PFAAs in humans, biota, or the environment (i.e., are PFAA precursors);*
- o *form PFAAs during combustion; or*
- o *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 current and 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 their life-cycle, including during product production, product use, and/or product end-of-life disposal/destruction. Concerns associated with fluoropolymers are illustrated in Lohmann et al. (2020; cited in the Product), which also is cited in the Product. Grouping PFASs as sub-groups within the class or even grouping them all together in one class is an approach that has been recommended by multi-authored publications (Cousins et al., 2020a ; not cited in the Product and Kwiatkowski et al., 2020; cited in the Product) and it is an approach that, for example, the European Union is considering (EU, 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 current and sound scientific knowledge, methods, and practices

Cousins et al. 2020a. Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health. Environmental Science Processes & Impacts. 22:1444-1460.

Commission Staff Working Document Poly- and perfluoroalkyl substances (PFAS), European Commission, SWD 249 final (2020).

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

Commission Staff Working Document Poly- and perfluoroalkyl substances (PFAS), European Commission, SWD 249 final (2020).

Cousins et al. 2020a. Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health. *Environmental Science Processes & Impacts*. 22:1444-1460.

Cousins et al. 2020b. The high persistence of PFAS is sufficient for their management as a chemical class. Environmental Science Processes & Impacts. 22:2307-2312.

Fenton et al. 2020. Per- and polyfluoroalkyl substance toxicity and human health review: Current state of knowledge and strategies for informing future research. Environmental Toxicology and Chemistry. https://doi.org/10.1002/etc.4890.

ITRC. 2020. Interstate Technology Regulatory Council. Ecological toxicology. https://pfas-1.itrcweb.org/7-human-and-ecological-health-effects-of-select-pfas/#7_2. Updated September, 2020.