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CalEPA Scientific Review Program

External peer review for the proposed adoption of carpets and rugs containing perfluoroalkyl or polyfluoroalkyl substances as a priority product and of the "Product – Chemical Profile for Carpets and Rugs Containing Perfluoroalkyl or Polyfluoroalkyl Substances"

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

In my review of the "chemical profile for carpets and rugs containing perfluoroalkyl or polyfluoroalkyl substances," hereby known as the "Product," I asked three questions of each of the *Conclusion 2*-specific points:

1) Does the science presented within the Product support each of the eight specific conclusions listed in the memo to the external peer-reviewers or of the Product as a whole?
2) Are there other sources not considered by the Product that would support a different conclusion for any one of the eight specific conclusions or of the Product as a whole?
   What are these sources and what different conclusion(s) would they support?
3) Are there different scientific interpretations of published data described within the Product? If so, what are those different conclusions?

Each point, below, reflects the application of these questions to each of the eight specific conclusions and for the Product as a whole. References cited are also included to support my external peer-review.

Conclusion 2-specific points addressed by the peer-reviewer

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

2) One of the putative reasons for the use of PFAS in myriad commercial and industrial applications is the strength of the carbon-fluorine bond. According to Buck et al. (2011): "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 article goes on to indicate 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…" (Buck et al. 2011). The lead author of this cited manuscript (which also is cited in the Product), Dr. Robert Buck, is chemist with a company that manufactures PFAS; remaining authors are chemists from various institutions. This manuscript reflects that there is agreement among leading PFAS chemists that PFAS 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 conclusion that PFAS are either extremely persistent or are PFAA precursors and hence have extremely persistent degradation products. is based on scientific evidence, presented in the Product, that demonstrate detectable concentrations of PFAS in environmental media (air, water, soil, biota) as well as support from the scientific community that PFAS are persistent in the environment.

3) 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 carpets and rugs by US EPA's significant new use rule (SNUR).

   The conclusion that longer-chain PFAS can bioaccumulate into living organisms is based on scientific evidence demonstrating that PFAS enter living organisms from environmental media (i.e., air, water, soil, food). Support for bioaccumulation comes from published bioconcentration, bioaccumulation, and/or biomagnification factors that identify values for such factors for PFAS that meet or exceed criteria for these values outlined in applicable California code. In addition, scientific evidence demonstrates that longer-chain PFAS 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 PFAS 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 PFAS in blood of umbilical cords, further supporting the transfer of PFAS from mother to offspring. When the persistence of PFAS also is considered in that PFAS in environmental media lead to continuous internal exposures in living organisms, traditional measures of bioaccumulation may underestimate PFAS accumulation into living organisms, including developing organisms exposed via the mother. Therefore, this conclusion is based on scientific evidence, presented in the Product, that PFAS can move from environmental media and into living organisms to produce a measurable internal concentration. Additionally, PFAS move from many types of environmental media, including air, water soil, and food, leading to internal exposures in living organisms that may exceed concentrations in any one environmental medium.

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

Accumulating scientific evidence for shorter-chain PFAS demonstrate that while they can bioaccumulate from environmental media, they are more rapidly excreted (i.e., in hours or days relative to years for some of the longer-chain PFAS) from living organisms, leading to relatively lower internal concentrations (Buck et al., 2011). Thus, a feature of shorter-chain PFAS is that they have shorter half-lives in living organisms. However, a feature of the shorter-chain PFAS is that they have increased mobility in the environment compared to longer-chain PFAS, potentially leading to a greater breadth of environmental contamination as well as exposures to living organisms. Therefore, the conclusion that shorter-chain PFAS possesses a potential hazard trait of concern (mobility), as presented in the Product, is consistent with the evidence amassed for shorter-chain PFAS.

5) The toxicological hazard traits of longer-chain PFAAs, which may still be present in imported carpets and rugs, have been well established in animal model and human epidemiologic studies. In humans, these include:
    a. Carcinogenicity (kidney and testicular cancers);
    b. Cardiovascular toxicity (increased serum cholesterol);
    c. Endocrine toxicity (thyroid disease);
    d. Immunotoxicity (immune dysregulation);
    e. Reproductive toxicity (pregnancy-induced hypertension).

    It should be noted that toxicological hazard traits of longer-chain PFAS listed for humans in this conclusion of the Product are mostly applicable to two PFAAs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) and come mainly from a large retrospective and/or prospective study of a single population exposed to drinking water contaminated with PFAS from an industrial site (the C8 Health Project). However, those leading this study had access to medical records of approximately 70,000 individuals and, based on water contamination and drinking water consumption data, were able to reconstruct past exposures (Shin et al., 2011). Additional prospective and cross-sectional studies of different human populations, including those from populations of high PFAS exposure and the general population, support many of the associations of the C8 Health Project and demonstrate that many different longer-chain PFAS can produce similar toxicological findings in exposed humans. Therefore, while the use of a single population exposed to a relatively small subset of PFAS may be considered insufficient to reach conclusions about the effects of PFAS on human health in general, supporting studies of other human populations exposed to many types of longer-chain PFAS and data from studies in animal models (discussed under #5) lend support to the C8 Health Project findings. Therefore, the conclusion that toxicological hazard traits of longer-chain PFAAs have been well established in animal model and human epidemiologic studies, is consistent with the evidence presented in the Product.

6) The toxicological hazard traits of the shorter-chain PFAAs are still emerging, based on more recent rodent, zebrafish, *in vitro*, toxicokinetic modeling studies. These include:
    a. Developmental toxicity (observed in zebrafish);
    b. Endocrine toxicity (PPAR-alpha activation *in vitro*);
    c. Hematoxicity (reduced red blood cell count, hemoglobin, and hematocrit in rodents);
    d. Hepatotoxicity (increased liver weight based on toxicokinetic modeling);
    e. Neurodevelopmental toxicity (suppression of neuronal differentiation *in vitro*);
    f. Ocular toxicity (delayed pupil response in rodents);
    g. 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 PFAS is less robust (i.e., there are fewer numbers of publicly available published studies) than the database for the longer-chain PFAS. However, it also is important to note that data contained in the publicly available publications emerging for the shorter-chain PFAS demonstrate that they produce a suite of toxicological hazard traits similar to the longer-chain PFAS. In fact, in the list of toxicological hazard traits identified in the Product that have been associated with the shorter-chain compounds, all have been reported for longer-chain compounds (ATSDR, 2018). Of particular concern are toxicological hazard traits associated with developmental, endocrine, and reproductive effects, as these hazard traits tend to affect populations and produce trans-generational outcomes that also lead to population-level outcomes. The following effects, while consistent with longer-chain PFAS, may not be the most robust indicators of toxicological hazard traits, but are still suggestive of the potential for shorter-chain PFAS to modulate biological responses: A) In the absence of histopathology or phenotypic outcomes, hematological outcomes typically reflect primary toxicity to other tissues and organs, such as the liver and kidney, as well as to the immune system, but are not always adverse outcomes themselves unless changes are seen in bone marrow or other aspects of blood function (Bloom et al., 2015). B) Increases in liver weight following PFAS exposure has been extensively debated in the scientific literature surrounding PFAS as some within the scientific community regard it as an adaptive response rather than an adverse response. For example, authors of a publication arising from a workshop of the European Society of Toxicologic Pathology, concluded that hepatomegaly as a consequence of hepatocellular hypertrophy without histologic or clinical pathology alterations indicative of liver toxicity was considered an adaptive and a non-adverse reaction. (Hall et al., 2012). C) While neurodevelopmental outcomes have been observed in some highly exposed human populations, the concordance between suppression of neuronal differentiation *in vitro* and human neurodevelopmental outcomes is tenuous, at best; such markers are useful as screening and prioritization tools but not as definitive indicators of adverse outcomes (Mundy et al., 2010). Individually, these three (A-C) outcomes are not definitive

indicators of toxicological hazard traits but taken together and along with data indicating that shorter-chain compounds can affect developmental, endocrine, and reproductive outcomes, they are supportive of the conclusion that short-chain PFAS can induce toxicological hazard traits, as described in the Product.

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

Accumulating scientific evidence for PFAS 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 PFAS and PFAA precursors can induce similar effects. There appear to be a paucity of data on environmental hazard traits in free-living aquatic and terrestrial wildlife species exposed to PFAS. There also appear to be a paucity of data from studies demonstrating an adverse impact finding of “negative,” (i.e., hazard traits were not evident in the results of the studies). However, a search of the literature in June of 2019 demonstrate that the majority of publicly available published wildlife studies for PFAS report internal blood and/or tissue-specific PFAS concentrations and not hazard traits. Therefore, the evidence as described in the Product appears to support that PFAAs display environmental hazard traits in a select number of environmentally-relevant wildlife models and in birds exposed in the wild.

8) PFAAs may have cumulative impacts with one another and with other hazardous chemicals.
For instance, one study found that PFHxA appears to enhance the adverse impacts of
PCB126. 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.

Humans and wildlife are exposed to mixtures of PFAAs, PFAS, 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 PFAS and/or PFAS mixed with other chemical compounds are limited, which is acknowledged in the Product. The Product presents findings from six different published studies of PFAS mixed with other chemical compounds, including polychlorinated biphenyls (PCBs), a variety of endocrine disrupting chemicals, heavy metals, 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. Therefore, as presented in the Product, this particular conclusion does not appear to be supported by the available scientific evidence to a great degree. There are suggestions, from the data, that additive and/or synergistic outcomes may arise from mixtures of PFAS or from PFAS mixed with other chemical compounds, but the data and the database are fairly weak at this point in time to indicate that such relationships are causative of adverse impacts. Therefore, the evidence as described in the Product appears to be weak with respect to the cumulative impacts of PFAS with one another and with other hazardous chemicals. However, as acknowledged in the Product, humans and wildlife are not exposed to single PFAS but mixtures of PFAS and are exposed to myriad other chemicals along with PFAS.

9) The adverse impacts associated with PFAAs are relevant to the entire class of PFASs because other PFAS either:
    a. Degrade to PFAAs in humans, biota, or the environment (i.e., are PFAA precursors);
    b. Form PFAAs during combustion; or
    c. 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 PFAS degrade to PFAAs, form PFAAs during combustion, or are manufactured using PFAAS and contain them as impurities is based on scientific evidence reporting detectable levels of PFAAs in degradation or combustion studies as well as knowledge of manufacturing processes involving PFAS. While certain PFAS, such as fluoropolymers, do not degrade in the same was as non-polymer PFAS, such as through environmental or metabolic degradation of precursor compounds, they can produce PFAAs at product end-of-life disposal/destruction, such as through combustion. In a recent review of how fluoropolymers differ from non-polymer PFAS that included a conclusion that fluoropolymers should not be grouped with other PFAS, the authors acknowledged that endof-life considerations should be further investigated (Henry et al., 2018). In other words, hazardous substances can arise from the combustion of fluoropolymers, which may include PFAAs. Therefore, the conclusion included in the Product appears to support that PFAAs can arise from a wide variety of PFAS and as PFAAs possess environmental hazard traits, PFASs themselves, through processes that lead to PFAAs, also possess environmental hazard traits.

General points addressed by the peer reviewer

a) In reading the product-chemical profile report and proposed implementation language, are there any additional scientific issues that are part of the scientific basis of the proposed regulation not described above? If so please comment.

The Product as well as the proposed implementation language appear to be thorough, complete, and comprehensive with respect to the scientific issues that are part of the scientific basis of the proposed regulation.

b) Taken as a whole, is the scientific portion of the proposed regulation based upon sound scientific knowledge, methods, and practices?

The scientific portion of the proposed regulation appears to be based upon sound scientific knowledge, methods, and practices. Only two areas, points #5 and #7 in the section on "*Conclusion 2*-specific points addressed by the peer-reviewer," appear to lack robust scientific support provided for the other points. 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 such cases, the proposed course of action is favored over no action. Thus, the proposed course of action is preferable over no action.

References included in this external peer-review

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