

## Review of “Carpets and Rugs Containing Perfluoroalkyl or Perfluoroalkyl Substances” as a Priority Product.

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### Focus of review

*Conclusion 2. Exposure to any PFASs used in carpets and rugs or to their degradation products, during product use or at its end-of-life, may contribute to or cause significant or widespread impacts to humans or biota.*

### Overall evaluation of Conclusion 2

PFASs used in carpet and rugs or their degradation products may contribute to widespread impacts to humans or biota. These compounds are found ubiquitously in the environment, and found in drinking water, surface water, waste water treatment facilities, food and indoor air and dust. PFASs are distinguished from most other organic contaminants by their extreme environmental persistence and long human half-life. PFASs, in particular longer-chain PFAAs such as PFOA and PFOS, causes several types of toxicity in experimental animals, including low dose developmental effects, some of which persist into adulthood. Biota including plants, aquatic species and birds exhibit toxicity, and due to bioaccumulation of certain PFASs they pose a potential environmental health risk, in particular to apex predators and endangered species. In humans, PFASs is associated with numerous health endpoints within the exposure range of the general population, as well as in more highly exposed or sensitive groups of individuals. As is the case for most such epidemiology studies, causality is not proven for these effects, but there are concerns. Infants are potentially a sensitive subpopulation for PFASs' developmental effects; exposure to infants, either directly or indirectly through breast milk, is higher than in adults. In summary, the information reviewed herein suggests that continued human and biota exposure to even relatively low concentrations of PFASs results in elevated body burdens that may increase the risk of health effects, and thus supports inclusion of carpets and rugs containing Perfluoroalkyl or Perfluoroalkyl Substances as a Priority Product.

Conclusion 2 is supported by the evidence for widespread exposure identified in Conclusion 1, and the following points:

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

This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature.

- *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).*

*This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature.*

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

*This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature.*

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

Although this statement is supported by this document and supporting literature, the lack of consideration of dose/exposure response information may lead the reader to conclude that these compounds are extremely toxic. In fact, the current human epidemiological data is not definitive, but is suggestive, especially in the range of exposures seen in the general public. In addition, most of the animal studies were conducted at high doses. Suggestions for how to more properly state the toxicology hazard traits summary will be given in the detailed review to follow and are summarized in the following statement.

- *The toxicological hazard traits of longer chain PFAAs, in particular PFOA and PFOS, which may still be present in imported carpets and rugs, have been established in animal and epidemiologic studies. These PFAAs can cause cancer, reproductive and developmental, liver and kidney, and immunological effects in laboratory animals while more limited findings related to infant birth weights, effects on the immune system and thyroid hormone disruption is seen in human epidemiological studies.*
- *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:*
  - *Developmental toxicity (observed in zebrafish);*
  - *Endocrine toxicity (PPAR-alpha activation in vitro)*

- Hematotoxicity (reduced red blood cell count, hemoglobin, and hematocrit in rodents),
- Hepatotoxicity (increased liver weight, based on toxicokinetic modeling);
- Neurodevelopmental toxicity (suppression of neuronal differentiation in vitro);
- Ocular toxicity (delayed pupil response in rodents); and
- Reproductive and developmental toxicity (fetal resorption and delayed eye opening in rodents).

A similar concern is shared with this statement. The following is more supportive by current literature.

- *The toxicological hazard traits of the shorter-chain PFAAs (including PFBS) are still emerging. Animal studies have shown health effects on the thyroid, reproductive organs and tissues, developing fetus, and kidney following oral exposure. Overall, the thyroid and kidney are particularly sensitive. The data are inadequate to evaluate cancer.*

Although it is suggested that these two points be rephrased to make the findings more concise, it does not change the interpretation of the document. The criteria for inclusion as a priority product is still supported, based on toxicologic hazard traits.

- *PFAAs display environmental hazard traits: phytotoxicity and wildlife development, or survival impairment.*

This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature

- *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 the other toxicants, even at doses at which the individual PFAAs and the other toxicants produced no observed adverse impacts*

This statement is not adequately supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature. The one study of PFHxA and PCB126 has not been repeated and the mixture studies do not show intersections of Adverse Outcome Pathways (AOPs) or Toxicology Pathways and hence difficult to interpret. Also, it is not necessary to support this document. It is suggested that this statement be deleted, as well as section within the document. Alternatively, this can be stated “PFAAs may have cumulative impacts with one another and with other hazardous chemicals, although co-exposures that dramatically affect adverse impacts are not know at this time”.

- *The adverse impacts associated with the 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*

This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature

### Moderate Editorial Comments and Concerns

#### Toxicological Hazard Traits

The list of toxicities seen in humans and animals does not reflect the current concerns for exposure and risk assessment. Although epidemiology studies have shown associations, they are weak or inconsistent. This needs to be noted. Many of the laboratory animal toxicity trends are seen at high doses, or are not a concern to human health. The following is a statement that reflects more accurately the toxicology hazard traits.

There is evidence that exposure to PFASs can lead to adverse health outcomes in humans. If humans are exposed to PFASs through diet, drinking water or inhalation they accumulate and stay in the human body for long periods of time. This, over time, the level of PFAS in their bodies may increase to the point where they suffer from adverse health effects. Studies indicate that PFOA and PFOS can cause reproductive and developmental, liver and kidney, and immunological effects in laboratory animals. Both chemicals have caused tumors in animal studies. The most consistent findings from human epidemiology studies are a small increase in serum cholesterol levels among exposed populations, with more limited findings related to: infant birth weights; effects on the immune system; cancer (for PFOA), and; thyroid hormone disruption (for PFOS). Some PFASs have also been linked to phytotoxicity, aquatic toxicity, and terrestrial ecotoxicity.

There is a general concern that the adverse effects listed for humans and animals are not do not consider dose- or exposure-effect relationships, as noted above. Instead of the list of effects, with no reference to exposure or internal dose, in Appendix II, it would be appropriate to show summary data with NOAEL/LOAEL data. Alternatively, another Appendix could be added with these values. Examples for PFOA are shown in Table 2 and 3 of G.B. Post et al. / Environmental Research 116 (2012) 93–117.

#### Minor Editorial Comments

(The following are meant to draw attention to minor typographical or grammatical errors or suggestions for clarification to the External Scientific Peer Review Draft)

Page 7, first paragraph. “PFASs released to the environment end up virtually everywhere in aquatic, atmospheric, and terrestrial environments, including remote locations far from any point source” is imprecise. Could be restated. “PFASs released to the environment are found in aquatic, atmospheric, and terrestrial environments, including remote locations far from any point source”

Page 7, second paragraph. “Because persistent PFASs lack a natural degradation route, their levels in the environment, humans, or biota may continue to rise for as long as PFASs are produced and used in consumer products.” Replace “may” with “will”.

Page 7, third paragraph “In the general population, PFAS exposure occurs mainly via ingestion of contaminated food and drinking water.” This negates the sentences that follow in which PFASs are released into dust and air. Several of the papers cited suggest that this inhalation may be significant depending on the number of carpets in the home or workplace. Consider adding “but other sources of exposure may contribute”

Page 7, third paragraph “Most (75% in 2016)...”. Delete “(75% in 2016)”.

Page 8, second paragraph. This should be re-written to acknowledge the gaps in knowledge and uncertainty. Many of the listed toxicities are higher dose or have not been consistently observed).

There is evidence that exposure to PFASs can lead to adverse health outcomes in humans. If humans are exposed to PFASs through diet, drinking water or inhalation they accumulate and stay in the human body for long periods of time. This, over time, the level of PFAS in their bodies may increase to the point where they suffer from adverse health effects. Studies indicate that PFOA and PFOS can cause reproductive and developmental, liver and kidney, and immunological effects in laboratory animals. Both chemicals have caused tumors in animal studies. The most consistent findings from human epidemiology studies are a small increase in serum cholesterol levels among exposed populations, with more limited findings related to: infant birth weights; effects on the immune system; cancer (for PFOA), and; thyroid hormone disruption (for PFOS). Some PFASs have also been linked to phytotoxicity, aquatic toxicity, and terrestrial ecotoxicity.

Page 16, 4<sup>th</sup> paragraph. “However, Kow ■ a common screening criterion of a neutral compound’s ability to partition from water into lipid-rich tissues within an organism (Mackay and Fraser 2000) ■ has limited applicability to PFAAs, due to their unique properties” Replace hyphens with commas.

Table 1. Unclear why PFOA has such a wide range of water solubility and vapor pressures.

Page 22, 3<sup>rd</sup> paragraph. “Few data on the aqueous photolysis of PFASs in water are publicly available; for instance but the half-life for 8:2 FTOH is  $93.2 \pm 10.0$  hours (Gauthier and Mabury 2005).” This sentence does not make a lot of sense. Perhaps just saying that there is little data on photolysis, but based on the stability of the compounds the half-life would be considered to be long would suffice

Page 22, 3<sup>rd</sup> paragraph. “PFAAs appear to not degrade at all under environmental conditions, even in activated sewage sludge”

Page 23, 2<sup>nd</sup> paragraph. “Longer-chain PFASs such as PFOS and PFOA are typically the predominant PFASs found in surface sediments (Rankin et al. 2016) “

Page 24, 3<sup>rd</sup> paragraph. “The tendency of PFAAs to bioaccumulate can partially be explained by (1) their higher affinity for phospholipids, which are major components of biological membranes, and (2) their similarity to fatty acids, which makes them bind to proteins within the organism (Ng and Hungerbühler 2014)”. This sentence should be deleted or restated. There is no evidence that PFASs have increased affinity for phospholipids (relative to other lipids) and the fact that they have a fatty acid structure has anything to do with the binding to proteins. Both of these facts are simply due to hydrophobicity.

Page 29, 4<sup>th</sup> paragraph “PFASs display multiple hazard traits according to the Office of Environmental Health Hazard Assessment (OEHHA)’s Green Chemistry Hazard Traits regulations (CAL. CODE REGS. tit. 22, §§ 69401 et seq.). These include toxicological hazard traits, (Articles 2 and 3), environmental hazard traits (Article 4), and exposure potential hazard traits (Article 5).” Rearrange the order of the document (2.3.1 Environmental persistence, 2.3.2 Toxicological hazard traits, 2.3.3 Environmental hazard traits) to reflect this order.

Page 30, 1<sup>st</sup> paragraph. There is no mention of PFOS in the discussion of persistence

Page 30, 3<sup>rd</sup> paragraph. “PFAAs can be transported across cross the brain blood barrier and accumulate are present in animal brain tissue (Greaves et al. 2013)”

Page 30, 4<sup>th</sup> paragraph “The placenta:maternal serum ratios of PFOS, PFOA, and PFNA were observed to increased during gestation — more so in pregnancies with male fetuses compared to female ones — suggesting bioaccumulation in the placenta and increasing exposure with fetal age (Mamsen et al. 2019) “ Remove hyphens, replace with comma.

Page 31, 2<sup>nd</sup> paragraph. “The global warming potential (GWP) of perfluoropolymethylisopropyl ether, a type of PFPEs, ranges from 7,620 over 20 years to 12,400 over 500 years, relative to CO<sub>2</sub> (IPCC 2007)” Define GWP or state whether this is a high value. Need context.

Page 31, 4<sup>th</sup> paragraph. “increased serum cholesterol (Skuladottir et al. 2015; Winquist and Steenland 2014)” Increased serum cholesterol is not an adverse event, it is a risk factor. The small increase in cholesterol have not been associated with an increase in cardiovascular disease.

Page 32, 3<sup>rd</sup> paragraph. “When differences in rodent toxicokinetics are taken into consideration,

PFECAs and shorter-chain PFAAs may have similar or higher toxic potency than the longer-chain PFAAs they are replacing. Using a toxicokinetic model and existing toxicity data sets, a recent study found that PFBA, PFHxA, and PFOA have the same potency to induce increased liver weight, whereas GenX is more potent (Gomis et al. 2018). The authors concluded that previous findings of lower toxicity of fluorinated alternatives in rats were primarily due to the faster elimination rates and lower distribution to the liver compared to PFOA and other longer-chain PFAAs.” This is not a useful interpretation for this assessment. The statement “The results of this study demonstrate that the apparent lower toxicity (toxicity assessment based on administered dose) of fluorinated alternatives in rats compared to legacy PFAAs was primarily caused by their faster elimination and lower distribution to the liver” is giving a reason for the difference in potency, nor negating the difference. This study has an impact in interpreting *in vitro* hepatotoxicity data (where toxicokinetics are eliminated), not *in vivo* data.

Page 32, 4<sup>th</sup> paragraph. “Activation of the nuclear peroxisome proliferation-activated receptor alpha (PPAR-alpha) is hypothesized as a mode of action that causes adverse health effects from PFAS exposure, but other biological interactions may be at play that have not yet been identified (Guyton et al. 2009; Rappazzo et al. 2017).”

There is concern about depicting PPARA activation as an important Mode of Action (MAO) of the toxicological profile of PFAAs. The human relevance of PPARA activation in rodent liver in respect to cancer is unclear. Importantly, the MOA(s) for neurobehavioral toxicity, delayed mammary gland development, and effects on the female reproductive tract are not known and would not include PPARA activation. PFOA and PFOS activate other nuclear receptors such as CAR (constitutive androstane receptor) and PXR (pregnane X receptor), which may be more important for the thyroid hormone metabolism effects. This could be restated... “The Mode of Action (MAO) of PFAAs have not been fully characterized. Activation of the nuclear receptor peroxisome proliferation-activated receptor alpha (PPAR-alpha) has been associated with some hepatic effects of PFOA and PFOS, although other biological interactions associated with neurobehavioral toxicity, delayed mammary gland development, and effects on the female reproductive tract not yet been identified (Guyton et al. 2009; Rappazzo et al. 2017).”

#### 2.4.1 Cumulative effects with other chemicals, starting on page 33

It is suggested that this section be deleted or that it be stated that very little data exists. Most of the studies depict additive effects (as expected for compounds that share MOAs) or were conducted in a manner that does not allow for a statistical examination of synergy (more than additive) or potentiation.

Page 34. Last paragraph. “In particular, longer- and shorter-chain PFAAs share three key structural and mechanistic properties: their structural similarity to fatty acids (DeWitt et al. 2015), their potential to activate PPAR-alpha (Rosenmai et al. 2018; Wolf et al. 2014; Wolf et al. 2008)”. See above, PPARA activation has limited meaning in terms of toxicity.

Page 36, 1<sup>st</sup> paragraph “Breasted infants are susceptible to increased exposures to PFASs in breast milk”. Change “Breasted” to “Breastfed”.

Page 50, 1<sup>st</sup> paragraph “In 2018 however, EFSA proposed to lower its TDI from 150 ng/kg body weight per day to 13 ng/kg body weight per week for PFOS, and from 1,500 ng/kg body weight per day to 6 ng/kg body weight per week for PFOA (EFSA 2018). According to EFSA, “exposure of a considerable proportion of the population” exceeds the proposed limits for both compounds (Knutsen et al. 2018). TDIs for other PFASs have not been established.” The low TDI and the low RfD in drinking water for these compounds set by government agencies is not highlighted in the summary/lay person description. Consider adding since this strengthens the overall rationale for prioritizing this product

Page 53, second paragraph “Nearly all humans ~~ever studied~~ show evidence of exposure to some PFASs”

Page 73, Adverse Impacts Linked to Exposure Potential Hazard Traits, Physicochemical Properties, and Environmental Fate. Within the list of exposure potential hazard traits, some mention should be made of exposure in drinking water (add to third bullet point or make one point).

Page 74-75. List of adverse impacts linked to toxicologic hazard traits. See previous discussions. The endpoints that have the lowest NOAEL are the most important, but there is not mention of potency in this section. If a table is added to an Appendix with NOAELs/LOAEL it should be referred to here. Some statement should be added to both lists that these adverse effects were seen at varying doses is different in vivo and in vitro models.

Page 74-75. Define what is meant by “long-chain” and “short-chain” PFAAs

Page 75, 2<sup>nd</sup> paragraph. “Studies have also suggested that PFAAs, including PFHxA, may contribute to mixture toxicity and enhance the adverse impacts associated with other hazardous compounds (see Section 2.4.1)” Delete sentence (see discussion above).

Page 75, 2<sup>nd</sup> paragraph. This statement may be considered alarming and is not discussed in previous sections. “The adverse impacts associated with PFASs can be widespread and significant. For instance, the total cost of hospitalization for medical concerns and loss of IQ points due to PFOA-attributable low weight births between 2003 and 2014 in the United States was estimated at \$13.7 billion (Malits et al. 2017).” To my knowledge, the association between birth weight and PFAAs is not established and there have been conflicting studies. The correlation between birth weight, IQ and hospitalization costs are questionable. I would recommend deleting.

Page 76, 1<sup>st</sup> paragraph. “Traditionally, the science of toxicology has been predicated on the principle that “the dose makes the poison.” However, the continuous emissions of mixtures of extremely persistent PFASs to contaminated media, even if in small amounts, could result in more frequent exposures at ever higher doses, with potential for significant adverse toxicological effects.” This is a vague sentence. Consider re-writing. “Due to the environmental persistence of PFASs, the continuous emissions of mixtures of PFASs results in an accumulation in contaminated media and increased risk for exposure. In addition, bioaccumulation and long biological half-life results in higher body burdens of PFASs and potential for adverse health effects”