Review of proposal to adopt a regulatory limit on "Plant Fiber-Based Food Packaging Containing Perfluoroalkyl or Polyfluoroalkyl Substances"

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John P. Vanden Heuvel, PhD
Professor of Molecular Toxicology
Department of Veterinary and Biomedical Sciences
Penn State University
University Park, PA

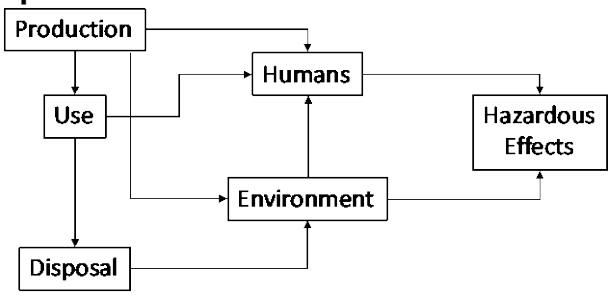
Focus of review

> ***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.***

Overall evaluation of Conclusion 2

PFASs used in food service packaging, such as plastic or fiber-based products, or degradation products therein may contribute to widespread impacts to humans or wildlife species. In food packaging, polyfluorinated coatings are used to impart water and fat repellency to the paper material. While the food is in contact with the paper the polyfluorinated compounds used and the PFAA residues and impurities might be distributed into the product contributing to human exposure. These compounds are also found ubiquitously in the environment, are detected in drinking water, surface water, waste water treatment facilities, food and indoor air and dust. It is generally believed that the majority of exposure to PFASs in humans is from food. PFASs are distinguished from most other organic contaminants by their extreme environmental persistence and long human half-life. PFASs, in particular longer-chain perfluoroalkyl acids (PFAAs) such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (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 are 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. Transplacental transport is a significant route of exposure to PFASs. 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 a regulatory limit on PFASs in plastic and fiber-based food service packaging.

Specific Evaluation of Conclusion 2



The goal of this evaluation was whether the scientific work product is "based upon sound scientific knowledge, methods and practices."

The examination of this conclusion required looking at all the potential sources of exposure to PFASs and their chemical structures that result from food service packaging (FSP) material as outlined in the figure below. Many PFASs have been detected globally in various components of the environment, such as biota, humans, and food items. PFASs used in the food service packaging may result in exposure to living systems *via* various direct and indirect pathways. Direct sources mainly include waste streams from manufacturing, and directly from the end product through use or disposal. PFAS-containing FSPs such as fast food packaging and microwave popcorn bags can contribute to indirect dietary exposure via migration into food. Prior studies of fast food packaging such as wrappers, paperboard, and paper cups found a wide range of PFASs, including PFOS and other perfluoroalkyl sulfonates (PFSAs), PFOA and other perfluoroalkyl carboxylates (PFCAs), fluorotelomer alcohols (FTOHs), and polyfluoroalkyl phosphate esters (PAPs). The extent of migration of PFASs from FSPs into food depends on the amount and chemical structure of the PFASs used, the type of food, contact time and temperature. Biotic and abiotic transformation of perfluoroalkyl precursors and the breakdown of perfluoroalkyl-based products represent indirect sources of contamination. FTOHs have been identified to be metabolized to PFOA and are thus a source of PFCAs and fluorotelomere precursors can be an indirect source of PFOA. For the purposes of this assessment, three major types of exposure to PFASs have been considered: general human exposure, occupational exposure, and prenatal and neonatal exposure.

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

- *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.*

This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature[1].

[1] Department of Toxic Substance Control. Product Chemical Profile, PFASs in Carpets and Rugs. 2018. Accessed February 3, 2020. https://dtsc.ca.gov/wpcontent/uploads/sites/31/2018/10/Product-Chemical-Profile-PFAS-Carpets-and-Rugs.pdf

- *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.*

Based on the available evidence, the toxicological hazard traits of longer chain PFAAs, which may still be present in FSP materials or indirectly produced, 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)

The toxicological hazard traits of the shorter-chain PFAAs, those derived from degradation of PFASs 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).
- 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.

In addition to the aforementioned effects above, there is an increased appreciation for developmental Toxicity caused by longer-chain PFCAs. PFCAs are able to cross the placenta-fetus barrier and have been observed in breast milk making *in utero* and lactational exposure to these compounds a significant concern. The relationship between maternal measured PFAS exposures during pregnancy (i.e. PFOS, PFOA, PFNA and PFHxS) and indices of fetal growth development including birth weight, birth length, gestational age and pre-term birth have been somewhat conflicting; however, the fact that several studies showed negative associations even at low dose exposure to PFCAs warrants further analysis. A recent prospective study shows an association between in utero exposure to PFOA and semen quality and reproductive hormones in male offspring

20 years later. These epidemiological studies, along with supporting data from several laboratory and wildlife animal studies indicate the developmental toxicity should be included in the panoply of hazard traits associated with longer chains PFCAs.

This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature[1].

- *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.*

This statement is supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature[1].

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

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- *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.*

This statement recognizes a data gap relevant to Conclusion 2

The fluorochemicals used in FSPs are blends or polymers and are often mixtures of homologue series of oligomers. Each mixture typically contains 3-10 structurally different molecules resulting up to 100 different polyfluorinated compounds. However, the composition or concentrations of PFAS in technical mixtures intended for use in FSP is not known. This hampers the development of confirmatory analysis of human exposure specifically from FCMs that is needed as input for quantitative risk assessment. There is a similar data gap concerning toxicological knowledge about the PFAS used in FSPs especially when it comes to the precursors used in production such as PAPs. This is true when addressing each individual PFAS as well as the overall hazard characterization of the FSP-derived fluorochemical mixture. In order to ascertain the cumulative effects (additive, synergistic or antagonistic) a better appreciation for mechanism of action of the PFASs is needed. For example, if the

majority of toxicity has the same molecular initiating event (i.e. interaction with PPAR), then one would expect an additive or cumulative toxicity contributed by each PFAS in the mixture.

In addition, PFAAs are believed to exist in complex mixtures with other xenobiotics. How the components of the mixture contribute to potential toxicity depends on the concentration of each substance as well as its mechanism of adverse events. As mentioned above, some co-pollutants may have additive, synergistic or antagonistic effects relative to PFAAs. For example, compounds such as phthalate esters are important pollutants and share some of the adverse effects and mechanism of action (PPARA activation) as PFAAs. The presence of phthalate esters may have an additive toxicologic response with longer chain length PFAAs. This effect may not be true for other classes of compounds such as insecticides that have different toxicologic sequalae.

This statement is **somewhat** supported by existing facts, as documented by Department of Toxic Substances Control (DTSC) and supporting literature[1] but is in need of more clarification and mechanistic understanding

- The adverse impacts associated with PFAAs are relevant to the entire class of PFASs because most 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[1].

Estimating health risks from exposure to FSP-derived PFASs
(Based on a similar discussion in Tier et al. [2])

Because of the data gaps mentioned above, in most instances we must rely on using prototypical PFASs to represent the entire class of compounds. In most instances, the PFCA compound PFOA is used to typify the family of PFASs due to the wealth of knowledge on both toxicity and exposure as well as it relative potency. The approach used by the US EPA is that of Minimal Risk Levels (MRL). The MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse, non-cancer health effects over a specified duration of exposure. MRLs are generally based on the most sensitive substance-induced end point considered to be

[2] Trier, Xenia; Taxvig, Camilla; Rosenmai, Anna Kjerstine; Pedersen, Gitte Alsing. PFAS in paper and board for food contact - options for risk management of poly- and perfluorinated substances. Copenhagen K, Denmark: Nordic Council of Ministers. TemaNord, No. 573. 2017. Accessed January 28, 2020. https://backend.orbit.dtu.dk/ws/portalfiles/portal/149769110/Rapport_PFAS_in_paper_and_board.pdf

of relevance to humans. Below is an example of the MRL determination of PFOA (from reference [3]). Note that this MRL is for all routes of oral exposure to PFASs, of which those derived from FSPs are included.

Selection of the Critical Effect: Intermediate-duration oral studies of PFOA in animals indicate that the liver, immune system, reproductive system, and the developing organism are the primary targets of toxicity because adverse outcomes were observed at lower doses than other effects and have been consistently observed across studies. A summary of the lower LOAEL values (and associated NOAEL values) for these tissues/systems is presented below; given the large number of studies, this table is limited to studies that identified LOAEL values of ≤4 mg/kg/day.

Summary of Potential Points of Departures (PODs) in Human Equivalent Doses (HEDs, ug/kg/day) for determination of Oral MRL for PFOA[3]

Hazard	Endpoint	Point of Departure (ug/kg/day)
Developmental	Decreased resting activity in mice	0.22
Developmental	Skeletal alterations in mice	0.24
Developmental	Altered novelty activity in mice	0.82
Immune system	Reduced response to DNP antigen in mice	1.2
Immune system	Increased severity of chronic inflammation in utero exposure to mice	1.2
Immune system	Reduced response to sRBC in mice	3.3
Reproductive	Decreased number of successful births in mice	8.4
Hepatic system	Increased liver weight, hypertrophy	13.5

MRL Summary: A provisional intermediate-duration oral MRL of $3x10^{-6}$ mg/kg/day was derived for PFOA based on altered activity at 5–8weeks of age and skeletal alterations at 13 and 17 months of age in the offspring of mice fed a diet containing PFOA on GD 1 through GD 21 (see above). The MRL is based on a LOAEL of 0.000821 mg/kg/day and a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

MRL Summary of other PFASs (from reference [4]).
Unsing approaches similar to that described above, Intermediate-duration (15-365 days) provisional oral MRLs were derived for

- PFOA: 3×10^{-6} mg/kg/day
- PFOS: 2×10^{-6} mg/kg/day
- PFHxS: 2×10^{-5} mg/kg/day

[3] ATSDR toxicological profile: Perfluoroctanoic acid https://www.atsdr.cdc.gov/toxprofiles/tp200-a.pdf

[4] ATSDR toxicological profile: Perfluoroctanoic https://www.atsdr.cdc.gov/toxguides/toxguide-200.pdf

- PFNA: 3 x 10^{-6} mg/kg/day

When comparing the amount of exposure to PFOA (based on measured serum levels) and the extrapolation of serum concentrations from the POD dose reached by Trier et al.[3] there are clear indications that the most exposed individuals among the general population are not protected from the hazardous effects of PFOA. As humans are exposed to several other PFAS and the human studies resulted in lower PODs than the rodent studies[4], adds additional concerns. For example, the POD concentrations calculation based on immunotoxicity (0.1 ng/mL) in children results in a reference dose that is times lower than that based on hypercholesterolemia in humans (0.73 ng/mL)[4].

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 a regulatory limit on PFASs in plant fiber-based food packaging