



Developmental and Reproductive Toxicant Identification Committee
c/o Tyler Saechao
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation Office
1001 I Street
P. O. Box 4010, MS-12B
Sacramento, California 95812-4010

November 15, 2021

RE: Consideration of Perfluorononanoic Acid (PFNA) and Perfluorodecanoic Acid (PFDA) and Their Salts for possible listing under Proposition 65 based on developmental reproductive toxicity

Dear Office of Environmental Health Hazard Assessment,

On behalf of the Natural Resources Defense Council and Clean Water Action, we appreciate the opportunity to submit comments on the proposal to list Perfluorononanoic Acid (PFNA) and Perfluorodecanoic Acid (PFDA) and their salts for possible listing under Proposition 65 based on developmental reproductive toxicity.

PFNA and PFDA, including their salts and transformation and degradation precursors are a serious public health threat due to their widespread occurrence, persistence, mobility and potential to cause health harms, including developmental and reproductive toxicity. Biomonitoring data in California show that PFNA and PFDA are readily detected in Californians¹ and monitoring data from the State Water Resources Control Board (SWRCB) show that they are consistently detected in the State's drinking water sources.²

OEHHA staff scientists have reviewed the available publications as of February 2021, and updated with additional publications as recently as November 5, and have prepared thorough documentation demonstrating that PFNA and PFDA and their salts should be listed as developmental and reproductive toxicants under Proposition 65.

A) Standards for DART IC to recommend listing a chemical under Proposition 65

¹ Biomonitoring California, *Results for PFASs*. <https://biomonitoring.ca.gov/results/chemical/2183>

² State Water Resources Control Board, *PFAS – Drinking Water Resources – Public Water System Testing Results*. https://www.waterboards.ca.gov/pfas/drinking_water.html

Pursuant to the regulations implementing Proposition 65, the Developmental and Reproductive Toxicant Identification Committee (DART IC) may “[r]ender an opinion . . . as to whether specific chemicals have been clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity.” 27 Cal. Code Regs. § 25305(b). The criteria that guide the CIC’s recommendations emphasize a “weight-of-evidence” approach and are “not intended to limit the scope of the Committee’s consideration of appropriate scientific information, nor to limit its use of best scientific judgment.”³ However, the criteria provide important indicators of the sufficiency of evidence that would support a recommendation for listing a chemical.

According to the criteria, “developmental toxicity,” “female reproductive toxicity,” and “male reproductive toxicity” are all included within “reproductive toxicity.” A chemical may be recommended for listing if it meets one of the following criteria:

- sufficient evidence of reproductive toxicity in humans, or
- limited evidence or suggestive evidence in humans, supported by sufficient experimental animal (mammal) data, or
- sufficient evidence in experimental animals (mammals), such that extrapolation to humans is appropriate.

Id. Male reproductive toxicity is defined:

. . . to include effects on the adult or, where appropriate, developing male organism, including, but not limited to:

- (1) Adverse effects on reproductive structure or function including:
 - a. Genetic damage to the spermatozoon or its precursors.
 - b. Impaired sperm and/or seminal fluid production, including alterations in sperm number, morphology, motility, and ability to fertilize.
 - c. Impaired or altered endocrine function.
- (2) Impaired reproductive performance (e.g., sub fertility, infertility, or impotence).

Id. The DART IC also takes account of biological plausibility and statistical considerations. *Id.* Considerations for sufficiency of evidence in humans include scientifically valid epidemiological studies conducted according to generally accepted principles, clinical cases, and weight of evidence considerations. *Id.* In animals, sufficiency of evidence considerations include: experimental design, relevance of exposure to expected human exposures and timing of exposure, number of dose levels sufficient to evaluate the presence of a dose-response relationship, maternal and systemic toxicity, number of tests or experimental animal species (including weight of evidence), and other considerations. *Id.*

The evidence for male reproductive toxicity presented by OEHHA, meets these criteria, and therefore the DART IC should recommend PFNA and PFDA and their salts for listing. In fact, the criteria justify the listing of PFNA and PFDA precursors as well, and the DART IC should also recommend the listing of the precursors.

B) PFNA and PFDA should be grouped with their salts and precursors for this listing

³ OEHHA, *Criteria for Recommending Chemicals for Listing as "Known to the State to Cause Reproductive Toxicity."* 1993.

As reviewed by OEHHA, the salt versions of PFNA and PFDA will dissociate in solution, releasing the PFNA and PFDA anions, respectively. Therefore, PFNA and PFDA have been used to refer to the acid and anion forms of both chemicals, as the anion and acid forms exist in equilibrium in aqueous solution. The management of PFAS chemicals with their salts is a scientifically valid and widely used approach.

PFNA and PFDA can also be formed by the transformation or degradation of a variety of perfluoroalkyl acid (PFAA) precursors, substances containing a PFAA moiety that may transform or degrade to terminal PFAA transformation products over time.

We note that the management of a PFAS chemical with its salts and precursors is a more comprehensive approach, often referred to as the “arrowhead approach.”⁴ We note that experts in the PFAS field have summarized different approaches for grouping PFAS, including the arrowhead approach. The extent to which these approaches are already in use in regulatory contexts throughout the world is discussed by the report authors. The authors note:

“The [arrowhead] approach represents the dominant current approach to grouping PFAS for risk assessment and risk management globally. Industry have used the approach in voluntary phase-out actions (e.g. 3M⁵) of PFAS chemistries and it is applied globally in PFAS regulations. For example, precursors to long-chain PFAAs have been grouped together with specific PFAAs in risk management (e.g. under REACH^{6,7} in the Stockholm Convention^{8,9} see [Table 1](#), or are currently under discussion, see [Table 2](#)) given that these precursor substances will transform to an “arrowhead substance of concern” (i.e. the long-chain PFAAs that have PBT properties) in the environment, in biota, or in humans.”

This shows that the arrowhead approach is generally accepted in the scientific community. As noted, the European Union is already using this approach. Further, other California agencies¹⁰ and state^{11,12} and federal¹³ legislatures are already regulating PFAS as a whole class.

OEHHA is proposing to use the arrowhead approach to list PFOS and its salts and precursors as carcinogens under Proposition 65. There is no reason to exclude precursors from this listing and OEHHA has not offered a reason for excluding precursors here. We strongly urge OEHHA

⁴ Cousins, I.T., et al., *Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health*. Environ Sci Process Impacts, 2020. **22**(7): p. 1444-1460.

⁵ 3M, *3M Phasing Out Some of its Specialty Materials*. 2000.

⁶ Vierke, L., et al., *Perfluorooctanoic acid (PFOA) — main concerns and regulatory developments in Europe from an environmental point of view*. Environmental Sciences Europe, 2012. **24**(1): p. 16.

⁷ ECHA, *ANNEX XVII TO REACH – Conditions of restriction. Entry 68. Perfluorooctanoic acid (PFOA)*. 2017.

⁸ Stockholm Convention, *PFOA, its salts and PFOA-related compounds draft risk profile*. 2015.

⁹ Stockholm Convention, *PFHxS, its salts and PFHxS-related compounds as well as polymers and mixtures*. 2018.

¹⁰ DTSC. *Effective July 1, 2021: Carpets and Rugs with Perfluoroalkyl or Polyfluoroalkyl Substances (PFASs)*. Safer Products 2021 [cited 2021 November 5]; Available from: <https://dtsc.ca.gov/scp/carpets-and-rugs-with-perfluoroalkyl-and-polyfluoroalkyl-substances-pfass/>.

¹¹ California Legislature. *An act to add Chapter 15 (commencing with Section 109000) to Part 3 of Division 104 of the Health and Safety Code, relating to product safety*. 2021394 AB-1200.

¹² The New York State Senate. *Relates to reducing the use of PFAS chemicals in firefighting activities*. 2019395 Senate Bill S439A.

¹³ US Congress. *National Defense Authorization Act for Fiscal Year 2020*. 2019396 S.1790.

to also include precursors for this listing as well, as it is critical that the state take steps toward class-based management of PFAS wherever possible.¹⁴

C) PFNA and PFDA and their salts and precursors are reproductive toxicants and should be listed under Proposition 65

OEHHA has clearly shown the weight-of-evidence supports listing PFNA and PFDA and its salts as male reproductive toxicants under Proposition 65. The DART IC guidance notes that male reproductive toxicity includes “adverse effects on reproductive structure or function” or “impaired reproductive performance” and that sufficient evidence in experimental animals, combined with limited evidence in humans and/or mechanistic evidence of reproductive toxicity supports listing.

There is sufficient evidence of reproductive toxicity in experimental animals, including, as specified in the DART IC criteria, adverse effects on reproductive structure or function,” such as “genetic damage to the spermatozoon or its precursors,” “impaired sperm and/or seminal fluid production, including alterations in sperm number, morphology, motility, and ability to fertilize,” or “impaired or altered endocrine function.” For instance, for PFNA, reductions in epididymal and testis weight, histopathological changes in the testis, reduction in epididymal sperm counts, and reduced serum levels were observed in rat and/or mouse studies. This was accompanied by results in human studies such as three of seven studies of effects of PFNA levels on serum testosterone (T) levels which reported decreases (including two, which were statistically significant), while the other four studies reported inconsistent results across locations or no associations with T. Similarly, for PFDA, this includes a National Toxicology Program study in which “dose-related reductions in testis and epididymis weights were observed in the NTP study in rats exposed to lower doses for 28 days (≥ 1.25 mg/kg-day).” And in human studies, “semen quality studies with the highest PFDA concentrations reported some associations with poorer semen quality.”

In addition to evidence of reproductive toxicity in animal and human studies, there is mechanistic evidence of reproductive toxicity for PFNA and PFDA. Key characteristics that are frequently exhibited by exogenous agents that cause male reproductive toxicity were recently identified, based on a survey of known male reproductive toxicants and established mechanisms and pathways of toxicity.¹⁵ Because endocrine-disrupting chemicals may be male reproductive toxicants, OEHHA also examines the set of key characteristics of endocrine-disrupting chemicals also developed recently based on knowledge of hormone actions and endocrine-disrupting chemical effects.¹⁶ The key characteristics approach provides a consistent, objective and systematic framework for identifying and evaluating mechanistic evidence and is consistent with the regulations’ focus on “generally accepted principles.”

OEHHA documents sufficient evidence for five out of eight key characteristics of male reproductive toxicity for PFNA and its salts (germ cells; alters somatic cells; alters production and levels of reproductive hormones; alters hormone receptors; is genotoxic) and seven out of

¹⁴ Kwiatkowski CF, et al. *Scientific basis for managing PFAS as a chemical class*. Environ Sci Technol Lett. 2020; 7(8):532-543.

¹⁵ Arzuaga X, et al. *Proposed key characteristics of male reproductive toxicants as an approach for organizing and evaluating mechanistic evidence in human health hazard assessments*. Environ Health Perspect. 2019; 127:065001.

¹⁶ La Merrill MA, et al. *Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification*. Nature Reviews Endocrinology 2020; 16:45-57.

ten key characteristics for endocrine disruption (interacts with or activates hormone receptors; antagonizes hormone receptors; alters hormone receptor expression; alters signal transduction in hormone responsive cells, factors and transcripts and activity; alters hormone synthesis; alters hormone distribution or circulating levels; alters fate of hormone producing or hormone responsive cells). Similarly for PFDA and its salts, OEHHA documents sufficient evidence of four out of eight key characteristics of male reproductive toxicity (alters germ cells; alters somatic cells; alters production and levels of reproductive hormones; alters hormone receptors) and six out of ten key characteristics for endocrine disruption (interacts with or activates hormone receptors; antagonizes hormone receptors; alters signal transduction in hormone responsive cells, factors and transcripts and activity; alters hormone synthesis; alters hormone distribution or circulating levels; alters fate of hormone producing or hormone responsive cells).

All of these categories of data are well-established and accepted scientific practice, consistent with the regulations' and the guidance's focus on generally accepted principles for assessing reproductive toxicity.

Conclusion

OEHHA used scientifically sound criteria to arrive at the conclusion to list PFNA and PFDA and their salts as male reproductive toxicants. In fact, we believe the evidence supports the listing of not only the salts, but also the precursors of PFNA and PFDA, and we urge OEHHA to also move to list the precursors.

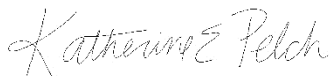
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