Carcinogen 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 5, 2021

RE: Consideration of perfluorooctane sulfonic acid (PFOS) and its salts and transformation and degradation precursors for possible listing under Proposition 65 based on carcinogenicity

Dear Office of Environmental Health Hazard Assessment,

On behalf of the Natural Resources Defense Council, we appreciate the opportunity to submit comments on the proposal to list perfluorooctane sulfonic acid (PFOS) and its salts and transformation and degradation precursors under Proposition 65 based on carcinogenicity

PFOS, including its salts and transformation and degradation precursors - or "PFOS and its salts and precursors" as referred to by OEHHA - are a serious public health threat due to their widespread occurrence, persistence, mobility and potential to cause health harms, including cancer. Biomonitoring data in California show that PFOS is readily detected in Californians and monitoring data from the State Water Resources Control Board (SWRCB) show that PFOS is a prevalent contaminant in the State's drinking water sources.

OEHHA staff scientists have reviewed the available publications as of February 2021 - in addition to a data call-in period from March 26 to May 10, 2021 - and the Proposed Public Health Goals (PHGs) for perfluorooctanoic acid (PFOA) and PFOS in drinking water[1] - and have prepared thorough documentation demonstrating that PFOS and its salts and precursors should be listed as carcinogens under Proposition 65.

[1] OEHHA, *Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water*. 2021.

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

Pursuant to the regulations implementing Proposition 65, the Cancer Identification Committee (CIC) 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 cancer." 27 Cal. Code Regs. § 25305(a). 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."[2] However, they provide important indicators of the sufficiency of evidence that would support a recommendation for listing a chemical.

According to the criteria, "if the weight of scientific evidence clearly shows that a certain chemical causes invasive cancer in humans, or that it causes invasive cancer in animals (unless the mechanism of action has been shown not to be relevant to humans), the committee will normally identify that chemical for listing."[3]

The CIC's guidance criteria outline various considerations for sufficiency of evidence for carcinogenicity in human and animal studies and includes general principles, such as General Principle F:

> "Whether evaluating the evidence for carcinogenicity in animals or humans, CIC members may make judgements utilizing other, more indirect, scientifically valid observations obtained using generally accepted methods and principles."[4]

In addition, OEHHA regulations for listing under the authoritative bodies listing mechanism, based on findings of authoritative bodies designated by the state's qualified experts—i.e., the CIC—state that:

. . . "as causing cancer" means that either of the following criteria has been satisfied:
(1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, "sufficient evidence" means studies in humans indicate that there is a causal relationship between the chemical and cancer.
(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, "sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset.

27 Cal. Code Regs. § 25306(e); see also 27 Cal. Code Regs. § 25904(b) (outlining similar criteria for listing of carcinogens based on findings by the International Agency for Research on Cancer (IARC)).

The evidence for carcinogenicity presented by OEHHA meets these criteria, and therefore the CIC should recommend PFOS and its salts and precursors for listing.

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[2] OEHHA, *Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer"*. 2001.
[3] Ibid.
[4] Ibid.

B) PFOS should be grouped with its salts and precursors for this listing

As reviewed by OEHHA, salts of PFOS will dissociate in solution, releasing the PFOS anion. Therefore, PFOS has been used to refer to perfluorooctane sulfonic acid and its anion, perfluorooctane sulfonate, as the anion and acid forms exist in equilibrium in aqueous solution. PFOS can also be formed by the transformation or degradation of a variety of PFOS precursors, defined by OEHHA as "substances containing the PFOS moiety (C8F17SO2) that may transform or degrade to PFOS."

The management of a PFAS chemical with its salts and precursors is a scientifically valid approach, often referred to as the "arrowhead approach."[5] We note that experts in the 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. 3M[6]) 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[7],[8] in the Stockholm Convention[9],[10] 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 agencies[11] and state[12,13]and federal[14] legislatures are already regulating PFAS as a whole class.

OEHHA has identified a non-exhaustive list of 169 PFOS precursors from authoritative sources, most of which lack data relevant to carcinogenicity. However, sources of PFOS include both direct emissions from manufacture, use and disposal, as well as indirect sources from the numerous precursor compounds that can undergo degradation and transformation to form PFOS. There is substantial evidence for these processes, both via abiotic and biotic

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[5] 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.
[6] 3M, *3M Phasing Out Some of its Specialty Materials*. 2000.
[7] 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.
[8] ECHA, *ANNEX XVII TO REACH – Conditions of restriction. Entry 68. Perfluorooctanoic acid (PFOA).* 2017.
[9] Stockholm Convention, *PFOA, its salts and PFOA-related compounds draft risk profile.* . 2015.
[10] Stockholm Convention, *PFHxS, its salts and PFHxS-related compounds as well as polymers and mixtures*. 2018.
[11] 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/.
[12] 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.
[13] The New York State Senate. *Relates to reducing the use of PFAS chemicals in firefighting activities*. 2019395 Senate Bill S439A.
[14] US Congress. *National Defense Authorization Act for Fiscal Year 2020*. 2019396 S.1790.

transformation under multiple relevant conditions, which is clearly outlined by OEHHA and extensively reviewed by others, including Buck et al. 2011.[15]

C) PFOS and its salts and precursors are carcinogens and should be listed under Proposition 65

OEHHA reports using systematic review methodology based on The Office of the Report on Carcinogens 2015 Handbook.[16] We support the use of systematic review methodology, and note the timeliness of completion of the report relative to when the literature search was conducted. The report was completed within 7 months of conducting the literature search and a call for additional data was made, ensuring the report reflects the most up-to-date data.

However, we note several areas for improvement in either the conduct or reporting of the systematic review. An important aspect of systematic review conduct is transparency. To this end, transparency would have been significantly increased if OEHHA had released a publicly available protocol detailing how this review would be conducted before work proceeded. If a protocol was developed it should, at a minimum, be made available as an Appendix to this report. Further, the inclusion and exclusion criteria that were used for study screening at both the title and abstract level and the full text level should be more explicitly stated either in section 2.2 or Appendix B. Currently the criteria are found in other sections that describe the results of the systematic review activities. It is also unclear how study quality was evaluated, for example, whether or not this was completed by two independent reviewers.

OEHHA has clearly shown the weight-of-evidence supports listing PFOS and its salts and precursors as carcinogens under Proposition 65. The CIC guidance notes that the "body of evidence shall include all evidence bearing on the issue of carcinogenicity shown through scientifically valid testing according to generally accepted principles." There are two main categories of evidence relevant to the carcinogenicity of PFOS and its salts and precursors.

The first is evidence of carcinogenicity in experimental animals, including, as specified in the CIC criteria, "an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments." This includes statistically significant increases in liver hepatocellular tumors, pancreatic islet cell carcinomas, mammary gland fibroadenomas and thyroid follicular cell adenomas in long-term carcinogenicity studies for PFOS potassium salt in rats,[17,18] and a tumor promotion study in rainbow trout that resulted in a statistically significant increase in liver tumor (adenoma and carcinoma combined) incidence.[19]

The second is mechanistic evidence of carcinogenicity. The key characteristics of carcinogens were developed from a comprehensive review of the more than 100 agents known to cause

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[15] Buck, R.C., et al., *Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins.* Integr Environ Assess Manag, 2011. **7**(4): p. 513-41.
[16] NTP, *Handbook for Preparing Report on Carcinogens Monographs* O.o.t.R.o. Carcinogens, Editor. 2015.
[17] Thomford, P.J., *104-Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Rats*. 2002: Madison, WI.
[18] Butenhoff, J.L., et al., *Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats.* Toxicology, 2012. **293**(1-3): p. 1-15.
[19] Benninghoff, A.D., et al., *Promotion of hepatocarcinogenesis by perfluoroalkyl acids in rainbow trout.* Toxicol Sci, 2012. **125**(1): p. 69-78.

cancer in humans.[20] The key characteristics approach provides a consistent, objective and systematic framework for identifying and evaluating mechanistic evidence and is consistent with General Principle F ("generally accepted methods and principles") as it is used by authoritative bodies, including IARC[21] and the Report on Carcinogens[22] to evaluate mechanistic evidence in the identification of carcinogens. OEHHA documents sufficient evidence for seven key characteristics of carcinogens for PFOS: is genotoxic, induces epigenetic alterations, induces oxidative stress, induces chronic inflammation, is immunosuppressive, modulates receptor-mediated effects, and alters cell proliferation, cell death, or nutrient supply; and some evidence for an additional key characteristic - causes immortalization.

Both of these categories of data--relying on evidence of carcinogenicity in animals and on mechanistic evidence of carcinogenicity--are well-established and accepted scientific practice, consistent with the regulations' and the guidance's focus on generally accepted principles for assessing carcinogenicity.

Conclusion

OEHHA used scientifically supported systematic review methodology and generally accepted, scientifically sound criteria to arrive at the conclusion to list PFOS and its salts and precursors as carcinogenic. We strongly support the listing of PFOS and its salts and precursors under Proposition 65.

Respectfully submitted,

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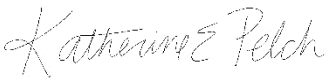

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[20] Smith, M.T., et al., *Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis.* Environ Health Perspect, 2016. **124**(6): p. 713-21.
[21] Samet, J.M., et al., *The IARC Monographs: Updated Procedures for Modern and Transparent Evidence Synthesis in Cancer Hazard Identification.* J Natl Cancer Inst, 2020. **112**(1): p. 30-37.
[22] Atwood, S.T., et al., *New Perspectives for Cancer Hazard Evaluation by the Report on Carcinogens: A Case Study Using Read-Across Methods in the Evaluation of Haloacetic Acids Found as Water Disinfection By-Products.* Environ Health Perspect, 2019. **127**(12): p. 125003.