November 8, 2021

Lauren Zeise, Ph.D.
Director
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street
Sacramento, California 95814

Re: Proposal to list perfluorooctane sulfonic acid (PFOS) and its salts and transformation and degradation precursors as carcinogens under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

Dr. Zeise:

The American Chemistry Council (ACC) submits the following comments on the proposal to list perfluorooctane sulfonate (PFOS) and its salts and transformation and degradation precursors as substances known to the state to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). ACC represents companies with an interest in the interpretation of the available scientific information on PFOS and related substances. ACC opposes the listing of PFOS as a carcinogen under Proposition 65.

As outlined below, the available data do not support a conclusion that PFOS presents a carcinogenic risk to humans. In the absence of epidemiological evidence and weak animal evidence, OEHHA's proposal to list is based primarily on 10 "key characteristics" of carcinogens proposed by Smith *et al.* (2016).[1] However, OEHHA has failed to demonstrate the predictive ability of these mechanistic assays including assay relevance, reproducibility/ reliability, specificity, and domain of applicability and predictivity. In fact, OEHHA staff have indicated that use of the key characteristics has been of "limited value for cancer hazard identification."[2] Likewise, there has been no plausible mode of action (MOA) proposed for PFOS exposure leading to cancer in humans[3]

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1 Smith MT *et al.* Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Persp* 124:713-721 (2016).

2 Sandy MS. Integrating information from multiple toxicity testing approaches in cancer hazard identification. Presentation at National Toxicology Program Converging on Cancer Workshop. April 29-30, 2019. https://ntp.niehs.nih.gov/events/webinars-workshops/2019/coc/presentations/index.html

3 Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. US Department of Health and Human Services, Atlanta, GA (2021). https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

Health and Safety Code § 25249.8 states "[a] chemical is known to the state to cause cancer . . if in the opinion of the state's qualified experts it has been *clearly shown through scientifically valid testing according to generally accepted principles* to cause cancer." (emphasis added). OEHHA guidance further provides that -

> a "weight-of evidence" approach shall be used to evaluate the body of information available for any given chemical. The body of evidence shall include all evidence bearing on the issue of carcinogenicity shown through scientifically valid testing according to generally accepted principles. . . Thus 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.[4]

Here, because the weight of scientific evidence does not clearly show that PFOS causes cancer in human or animals, OEHHA relies on the key characteristics identified by Smith *et al.* This approach, however, cannot meet the standard of "scientifically valid testing according to generally accepted principles." In fact, a 2017 analysis of high-throughput screening results for over 200 substances that have been reviewed by the U.S. Environmental Protection Agency (USEPA) for carcinogenic potential found that the use of the key-characteristics approach was "no better than chance" in predicting cancer.[5] Therefore, OEHHA's reliance on this approach, in the absence of evidence of the ability to predict carcinogenic potential, is arbitrary, capricious, and entirely lacking in evidentiary support.[6]

The epidemiological data indicate no association of PFOS exposure with liver, pancreatic, or prostate cancer or of cancers of the digestive, respiratory, lymphatic, or hematopoietic systems; the evidence for breast cancer is inconclusive and at times contradictory. The animal evidence is limited to a single chronic exposure study suggesting liver tumors resulting from a mode of action that is likely of little relevance to humans. Both the European Food Safety Authority (EFSA)[7] and Health Canada[8] have concluded that the available evidence does not support the carcinogenicity of PFOS.

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4 https://oehha.ca.gov/media/downloads/crnr/revcriteria.pdf

5 Becker RA *et al.* How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? *Reg Toxicol Pharma* 90:185-196 (2017). http://doi.org/10.1016/j.yrtph.2017.08.021

6 See *Exxon Mobil Corp. v. Office of Environmental Health Hazard Assessment*, 169 Cal. App. 4th 1264, 1277 (2009).

7 EFSA. Risk to human health related to the presence of perfluoroalkyl substances in food. Panel on Contaminants in the Food Chain. *EFSA Journal* 18(9):6223 (2020).

8 Health Canada. Guidelines for Canadian Drinking Water Quality. Guideline Technical Document – Perfluorooctane Sulfonate (PFOS). Ottawa, Ontario (December 2018). https://www.canada.ca/en/health-

Epidemiological Data

Several studies have attempted to assess cancer incidence in populations exposed to PFOS, including both occupational and community studies. The worker studies have focused on a fluorochemicals production facility in Alabama. Significant community studies include populations in France, Denmark, Sweden, Holland, Taiwan, and Greenland. These studies show no association of PFOS with liver, pancreatic, or prostate cancer or of cancers of the digestive, respiratory, lymphatic, or hematopoietic systems. While Alexander et al. (2003) reported an increase in in bladder cancer in the worker population in Alabama,[9] a more detailed follow-up study found no association with bladder cancer and PFOS exposure.[10] No increase in breast cancer incidence was observed among 263 female employees at the production facility in Alabama,[11] although the number of cases was too small for further analysis.

Several community studies have investigated the association with breast cancer and have reported mixed results. In general, the number of cases investigated in these studies has been relatively small – significantly limiting their interpretation. Two recent case-control studies have investigated the hormone receptor status among women with breast cancer in France and Taiwan. Both have suggested an association between PFOS exposure and estrogen receptor positive (ER+) tumors, the most diagnosed tumor type. In both studies, the analysis was based on a single blood sample which, in the case of the study of French women was collected several years before cancer diagnosis. PFOS levels vary widely between the two studies, with the blood collected in the Taiwan study between 2013 and 2015 – well after the voluntary phase out of PFOS in Japan, Europe, and the US. As a result, the relevance of the PFOS blood levels is uncertain.

Mancini *et al.* (2020) investigated breast cancer incidence in 194 post-menopausal women (mean age of diagnosis – 68.8, range 58.3 to 84.9) diagnosed prior to 2013 for which a single blood sample had been collected between 1994 and 1999.[12] No summary data on PFOS levels is provided, but levels ranged from 5.8 to 13.6 nanograms per milliliter (ng/mL) in the lowest quartile of serum level to 22.5 to 85.3 ng/mL in the highest quartile. Mancini *et al.*

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canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate.html

9 Alexander *et al.* Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occup Env Med* 60:722-729 (2003).

10 Alexander BH and Olsen GW. Bladder cancer in perfluorooctanesulphonyl fluoride manufacturing workers. *Ann Epidem* 17:471-478 (2007).

11 Grice M *et al.* Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. *J Occup Environ Med* 49(7):722–729 (2007).

12 Mancini FR *et al.* Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case-control study in the French E3N cohort. *Intl J Cancer* 146:917-928 (2020).

report no association with breast cancer incidence in their adjusted model including eight covariables (Model 1), and an association for quartiles 2 and/or 3 but not quartile 4 in the unadjusted and two other adjusted models (Models 2 and 3). In all, 15 covariables were included in Model 3. The association with ER+ tumors was only observed in adjusted Model 3 where the inclusion of so many covariables results in wide confidence intervals, limiting the study's power.[13]

In a study of Taiwanese women, Tsai *et al.* (2020) observed an association between PFOS levels and the incidence of breast cancer overall and for ER+ tumors in 120 woman less than 50 years old (mean age of 48.9 at diagnosis).[14] The mean serum level in the women was 5.64 ng/mL, which represents the lowest serum level quartile in the study by Mancini *et al.* Contrary to the results of the Mancini study, there was no association with breast cancer or ER+ tumors in woman over the age of 50 – despite the fact these women were likely to have experienced higher overall exposure to PFOS. Interpretation of these results is complicated by an overall increase in breast cancer incidence among younger women in Taiwan and other East Asian countries which has been associated with a reduction in the number of births and an increase in the child bearing age of the women.[15] The study also may be complicated by exposure to other pollutants.

Animal Carcinogenicity Data

Only one chronic animal bioassay has been performed for PFOS. The study exposed Sprague-Dawley rats to up to 20 parts per million (ppm) K+PFOS in their diet (daily dose of 0 to 0.984 milligrams/kg in males and 0 to 1.251 mg/kg for females) for 2 years.[16] Carcinogenic effects in the study included tumors in the liver, thyroid, and mammary gland.[17] An increased incidence of total hepatocellular adenoma, statistically significant at the highest dose, was observed in both sexes in rats exposed for 2 years. The increased incidence of hepatocellular

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[13] Tumor hormone receptor expression was available for 158 of the 194 cases (81%). Of these, 132 tumors (83%) were ER+.

[14] Tsai M-S *et al.* A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. *Environ Intl* 142:105850 (2020).

[15] Chen SL *et al.* Childbearing and quality of life decisions for women in Taiwan. *Intl J Healthcare* 4:16-24 (2018). Cited in Tsai *et al.*

[16] Butenhoff *et al.* Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. *Toxicol* 293(1-3):1-15 (2012). The study also included a recovery group exposed to 20 ppm for the first 52 weeks and then to the control diet through study termination.

[17] Contrary to the information provided in the evidence summary prepared by OEHHA, Butenhoff *et al.* provided no data on pancreatic islet cell carcinomas although the authors indicate that pancreas tissue was collected and analyzed.

adenomas in the male and female rats and of combined adenomas/ carcinomas in the females, however, did not display a clear dose-related response.

A statistically significant increase in the incidence of hepatocytic necrosis and hypertrophy in both males and females observed in this study and in short-term studies,[18] combined with evidence of PPARα and CAR/PXR activation,[19] suggests that the liver tumors observed in the rats may be of limited relevance to humans. The authors concluded that the liver effects were consistent with PPARα and CAR/PXR activation and that the available human and animal data "do not provide support for cancer risk from exposure to PFOS." Minimal changes in histology and clinical chemistry provide further evidence that the liver tumors reported are likely to be a rodent-specific phenomenon.[20]

Dose-response and temporal patterns for thyroid and mammary gland tumors were less consistent. Thyroid follicular cell adenomas were increased in males exposed to the highest dose for 52 weeks, but not in males exposed to the same dose for the full 2 years of the study. Combined thyroid follicular cell adenomas and carcinomas were increased only in females in the second-highest exposure group (5 ppm), but not in high-dose females. The significance of these neoplastic lesions to humans is also uncertain, as rodents have been shown to have a unique sensitivity to thyroid follicular hyperplasia (leading to development of follicular tumors) that is considered less relevant to humans.[21]

The incidence of mammary fibroadenoma and combined fibroadenoma/adenoma was increased only in the lowest dose of females (0.5 ppm) and showed a significant negative trend for both fibroadenomas (p=-0.0152) and combined fibroadenoma/adenoma (p=-0.0239). Pairwise comparison between the control and the highest dose group also was negative for both fibroadenoma and fibroadenoma/adenoma.

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[18] Seacat AM *et al.* Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicol* 183:117-131 (2003).

[19] Elcombe CR *et al.* Hepatocellular hypertrophy and cell proliferation in Sprague–Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPARα and CAR/PXR. *Toxicol* 293(1-3):16-29 (2012).

[20] Hall AP *et al.* Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes – conclusions from the 3rd International ESTP expert workshop. *Toxicol Pathol* 49(7):971-994 (2012) https://doi.org/10.1177/0192623312448935

[21] US Environmental Protection Agency. Assessment of thyroid follicular cell tumors. EPA/630/P-02/002F. Risk Assessment Forum. Washington, DC (1998). https://www.epa.gov/sites/production/files/2014-11/documents/thyroid.pdf

Mechanistic Considerations

Supporting documentation developed by OEHHA staff also reviews the findings from studies examining the effects of PFOS on seven characteristics identified by Smith *et al.* Consideration of these characteristics, however, does not provide a chemical-specific pathway characterizing events between exposure via specific route and an adverse outcome in a given domain of applicability. Consequently, they cannot be used to identify an MOA and serve only as a means to organize information about general characteristics.

Although the application of these characteristics may be useful for identifying and organizing relevant data, it is critical that they be combined with an understanding of the plausibility and causal linkages of the sequence of key events and biological responses involved in carcinogenesis.[22] Without a critical evaluation and integration of the mechanistic evidence with the other realms of evidence, moreover, application of the identified characteristics is of limited value in supporting a scientifically defensible conclusion of carcinogenicity.[23] A more accepted approach is to gather available information to develop a MOA demonstrating causation of cancer. According to the World Health Organization International Program on Chemical Safety, a MOA for carcinogenesis is "a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data."[24] OEHHA has presented no information outlining a proposed MOA or data from experimental observations to support causation of cancer in humans from PFOS exposure.

Assertions that a suspicion of carcinogenic potential can be inferred by bioactivity in one or more assays mapped to key characteristics of carcinogens are not based on rigorous scientific analysis. To inform risk assessment, extensive scientific analyses are required to interpret non-targeted experimental findings from molecular and cellular assays relative to the potential for human health risk – an exercise for which best practices have not been established. Use of non-targeted approaches, such as the key characteristics, without integration into an appropriate causal framework, are insufficient for hazard identification and risk assessment. Many scientists have published on the limitations of the key characteristic approach as it relates to directly informing decision making and risk assessment, particularly considering the lack of validation of the concept as a predictive tool.[25]

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[22] Becker *et al.* How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? *Reg Tox Pharma* 90:185-196 (2017). http://dx.doi.org/10.1016/j.yrtph.2017.08.021

[23] Goodman J and Lynch H. Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. *Toxicol Appl Pharma* 319:39-46 (2017). https://doi.org/10.1016/j.taap.2017.01.020

[24] Boobis AR *et al.* 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. *Crit Rev Toxicol* 36(10):781-792 (2006). https://doi.org/10.1080/10408440600977677

[25] See for example: Fielden M *et al.* Modernizing Human Cancer Risk Assessment of Therapeutics. *Trends in Pharma Sci* 39(3):232-247 (2018) https://doi.org/10.1016/j.tips.2017.11.005; Guyton, KZ *et al.* Application of

The limitations of the key-characteristics approach have been highlighted by two recent publications. The first by Bus reviews the challenges in the use of oxidative stress as a key characteristic in the evaluation of glyphosate by the International Agency for Research on Cancer (IARC).[26] The second publication by Becker *et al.*[13] applied the key characteristics to the data from high-throughput studies[27] for about 250 chemicals evaluated for carcinogenicity by USEPA's Office of Pesticide Programs for which ToxCast/Tox21 data are available. The authors conclude that the ability to predict cancer hazard by applying the key characteristics, alone or in combination, with the high-throughput data was "no better than chance." Moreover, interpretation of in vitro assays is complicated by the surfactant properties of PFOS and other PFAS.[28]

As outlined above, the available information does not support consideration of PFOS for listing as a carcinogen under Proposition 65. Please feel free to contact me at 202-249-6727 or at srisotto@americanchemistry.com if you have questions about the information provided in this letter or wish to discuss the information in more detail.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

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the key characteristics of carcinogens in cancer hazard identification. *Carcinogen* 39(4):614–622 (2018) https://doi.org/10.1093/carcin/bgy031; Wikoff DS *et al.* A framework for systematic evaluation and quantitative integration of mechanistic data in assessments of potential human carcinogens. Toxicol Sci 167(2):322–335 https://doi.org/10.1093/toxsci/kfy279

[26] Bus JS. IARC use of "oxidative stress" as key mode of action characteristic for facilitating cancer classification: glyphosate case example illustrating a lack of robustness in interpretative implementation. *Regul Toxicol Pharma* 86:157-166 (2017). https://doi.org/10.1016/j.yrtph.2017.03.004

[27] The USEPA's ToxCast program and the Tox21 federal agency collaboration.

[28] Singh N and Hseih CYJ. Exploring potential carcinogenic activity of per- and polyfluoroalkyl substances utilizing high-throughput toxicity screening data. *Intl J Toxicol* 40(4):355-366 (2021). https://doi.org/10.1177/10915818211010490