August 29, 2023

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Re: Public Health Goals - Second Public Review Draft for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water (July 2023)

Dear Dr. Khan:

The American Chemistry Council (ACC) submits the following comments on the second public review draft of the proposed Public Health Goals (PHGs) for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS).[1] ACC notes that the second draft is little changed from the draft PHGs released in July 2021. ACC raised a number of significant concerns with the 2021 draft that are summarized below and supplemented with information that has become available since that time. We note that several recent publications were not included in the second review draft and have enclosed a list of a few recent publications that should be added to OEHHA's review.

As in the 2021 draft, the Office of Environmental Health Hazard Assessment (OEHHA) has proposed PHGs for PFOA and PFOS of 0.007 parts per trillion (ppt) and 1.0 ppt, respectively, based on evidence of carcinogenic potential. The PHG proposed for PFOA relies on epidemiology studies with limited information on exposure and questionable findings while the draft PHG for PFOS relies on the results of animal cancer bioassays that were not statistically significant or that are consistent with rodent-specific effects. In calculating the draft PHGs, moreover, OEHHA has strayed from the approach outlined in its 2009 guidance by including unnecessary or overly conservative assumptions in the application of benchmark dose methodology and in estimating the relative source contribution from drinking water.

Considering the conflicting evidence for PFOA, and very limited information for PFOS, the PHGs for these two substances should be reassessed based on non-cancer health end points that are supported by the available science. As described below, however, the data OEHHA has selected for the proposed non-cancer PHGs are not supported by the evidence of health effects in epidemiology studies.

[1] OEHHA. Public Health Goals - Second Public Review Draft for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water (July 2023). (PHG Draft)

OEHHA Cannot Conclude that PFOA is Likely to be Carcinogenic to Humans

OEHHA proposes to establish a PHG for PFOA based on reports of elevated levels of kidney cancer by Shearer *et al.* (2021)[2] and Vieira *et al.* (2013).[3] However, these findings are not supported by the results from another study where the potential for exposure to PFOA was better characterized. Although human data are preferable to animal results in assessing potential health effects, a number of practical and resource constraints generally limit the ability for risk assessors to use epidemiological evidence for developing quantitative risk values.[4] These factors are described in more detail for the individual studies selected by OEHHA, but include uncertainty about exposure, consideration of confounding factors, and adequate sample size. As a result, epidemiology is generally used to complement the animal data in corroborating or clarifying the carcinogenic potential of a substance.

In the case of PFOA, however, the human cancer profiles are not consistent with observations of cancer in animal studies and in fact, contradict the animal results, without any biological plausibility or underlying mode of action differences attributable to the species under study. When this kind of disconnect occurs, further study is necessary to explain why the information generated in rodent studies is not consistent with the disease progression in humans. This lack of consistency across species undermines confidence in the use of cancer as suitable endpoint for human risk assessment.

Shearer *et al.* (2021) – Multi-Site Case-Control Study

Shearer *et al.* identified 324 cases of renal cell carcinoma (RCC) among 75,000 participants of a multi-site study from medical centers in ten US cities.[5] The subjects had baseline serum collected during 1993-2002, although the samples were not analyzed for PFOA until 2018. The cases were diagnosed with RCC subsequent to serum collection. A control group of 324 individuals who never had RCC was selected from among the same study participants – matched to the RCC cases by age (>50 years of age), sex, ethnicity, study center, and year of blood draw.

The researchers calculated odds ratios (ORs) for exposure quartiles and for continuous exposure, controlling for multiple potential confounding factors[6] in addition to the case-control

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2 Shearer JJ *et al.* Serum concentrations of per-and polyfluoroalkyl substances and risk of renal cell carcinoma. *J Natl Cancer Inst* 113:580-587 (2021).

3 Vieira VM *et al.* Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. *Environ Health Perspect* 121(3): 318-323 (2013).

4 US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. EPA/630/P-03/001F (2005). https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

5 The total population of 150,00 individuals was divided into two groups – screening and control. RCC cases and controls were identified from the screening group.

6 These included body mass index, smoking status, hypertension, prior freeze-thaw cycle, year of blood draw, estimated glomerular filtration rate (eGFR), and exposure to other PFAS. Several of these confounders are on

matching factors. The quartiles were assigned based on serum concentrations of PFOA among controls, resulting in an uneven distribution in the ranges of the quartiles which can skew the analysis for exposure-response trends. As shown in **Table 1**, the data do not support a positive dose-response relationship and would be considered not significantly elevated (*i.e.*, CI includes 1.0) for the three higher exposure quartiles after adjusting for other PFAS exposure. The results also do not suggest a dose-response pattern, and the p value for a positive trend was not statistically significant (p=0.13) according to the researchers.

Table 1. Odds ratios and 95% confidence intervals (CIs) evaluating PFOA serum concentration and risk of renal cell carcinoma (Shearer *et al.* 2021)[7]

Serum Concentration Quartile (micrograms/Liter)	Controls	Cases	OR	95% CI
<4.0	81	47	1.00	Reference
>4.0-5.5	79	83	1.41	0.69, 2.90
>5.5-7.3	83	69	1.12	0.52, 2.42
>7.3-27.2	81	125	2.19	0.86, 5.61
Continuous[8]			1.68	1.07, 2.63

Shading is applied to demonstrate that the 95%CI range includes the odds of 1.00, meaning the finding is *not statistically significant* and is not found to be a significantly elevated odds ratio.

Although the OR for the continuous exposure analysis was statistically significant, questions remain about the significance of this finding. Of primary concern is whether the single serum measurement taken prior to RCC diagnosis (1993-2002) is representative of exposures over an extended period of time.

Conducting an analysis for continuous exposure, in addition to the quartile analysis, helps to address the disparity in the range of the exposures in the quartiles. However, questions remain about the distribution of exposures between the two groups. The serum PFAS concentration contrasts in Shearer *et al.* study were relatively small, as they reflect general population levels (the lowest PFOA concentration quartile was less than 4 nanograms/milliliter (ng/ml), while the uppermost was greater than 7.3–27.2 ng/ml).[9] The supplemental information[10] provided by

their own dose-response continuum, rather than a simple yes/no comparison, which further complicates the ability to pinpoint the effects of PFOA exposure.

7 Source: Table 2 of Shearer *et al.* 2021.

8 Continuous OR is in relation to a 1-unit increase in serum PFOA concentration on the log base 2 scale.

9 Steenland K and Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. *Environ Res* 194:110690 (2021).

10 https://academic.oup.com/jnci/article/113/5/580/5906528#supplementary-data

Shearer *et al.* suggests that the range of serum levels was only slightly higher among the cancer cases compared to the controls, with the exception of a single serum level nearly 10 times the high end of the range in the case group. While this value may explain the use of a log base 2 scale for the continuous analysis, the authors do not explain the potential effect of this outlier on their results. However, the broad confidence interval in the highest exposure quartile suggests that such an explanation is necessary to adequately interpret the findings. Typical publications of this type will generally develop an equation that explains the relationship between the continuous variables, as well as provide a robust uncertainty or sensitivity analysis. These elements are missing from the Shearer *et al.* publication and would be considered best practice for epidemiology that is expected to become the basis for a public health regulation.

Although the researchers were able to use several factors to match controls to the RCC cases, the decision to select an equal number of controls may also limit the significance of the continuous exposure finding. The number of controls selected per case may vary, but it is common in the nested case-control literature to find four or five controls per case.[11] The researchers do not provide an explanation for the decision to identify only 324 controls, particularly given the fact that they appear to have had such a large pool of individuals for whom a serum sample had been collected.

These concerns are echo]ed by EPA[12] which identified deficiencies in controlling for confounding and adequate confidence in selectivity and sensitivity in the study by Shearer *et al.* Based on "several limitations of the Shearer (2021) study," EPA's Science Advisory Board (SAB) questioned the decision to use its results as the sole basis for the cancer slope factor (CSF).[13] Because the CSF derived from this study is two to three orders of magnitude more potent than that derived from experimental animal studies, SAB cautioned that "the decision as to what slope factor to recommend needs to be carefully considered and highly transparent."

Vieira *et al. 2013* – Mid-Ohio River Valley

The second study used in the derivation of the PHG by Vieira *et al.* is one of two publications to explore cancer outcomes among residents living near a fluoropolymer manufacturing plant in Parkersburg, WV. A second publication by Barry *et al.* (2013) extended the analysis of outcomes for an additional number of years.[14] In their study, Vieira *et al.* identified cases of kidney and 17 other

[11] Ernster VL. Nest case-control studies. *Prevent Med* 23(5):587-590 (1994). https://doi.org/10.1006/pmed.1994.1093

[12] USEPA. Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water. Public Comment Draft. EPA Document No. 822P23005. Office of Water (2023), at 3-265. https://www.regulations.gov/docket/EPA-HQ-OW-2022-0114

[13] USEPA SAB. Review of EPA' Analyses to Support EPA's National Primary Water Rulemaking for PFAS. EPA-SAB-22-008 (2022), at 38. https://www.regulations.gov/docket/EPA-HQ-OW-2022-0114

[14] Barry V *et al.* Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect* 121(11-12):1313-1318 (2013).

cancers among residents of the 13 counties surrounding the manufacturing facility. ORs were calculated based on estimated PFOA serum levels for the contaminated water districts in OH and WV and for individual residences in OH using a PFAS exposure model and serum data collected from the C8 Health Project in 1995. The control groups were composed of individuals with cancers other than those that have been linked to PFOA exposure.[15]

A total of 751 cases of kidney cancers were diagnosed between 1996 and 2005 in the 13 counties – 505 in WV and 246 in OH. The control groups totaled more than 23,000 for the water district analysis and over 7,000 for the analysis of serum concentration among OH residents. In the water district analysis, residents within a district were assumed to have a serum concentration equal to the median concentration for that district; individuals outside these districts were considered to have no PFOA exposure. The OR for the two water districts with the highest estimated serum concentrations was not significantly elevated (the CI included 1), nor was the OR for the total exposed group, after adjusting for several confounding factors.[16]

For the analysis by individual OH residence, serum levels at the time of diagnosis and 10 years prior to diagnosis were estimated based on the street address. Cumulative PFOA exposure was estimated based on estimated drinking water levels Individuals were categorized into quartiles of estimated serum concentration and adjusted ORs were calculated for each quartile compared to the unexposed group. As shown in **Table 2**, adjusted ORs for the low and medium do not support a positive dose-response relationship for kidney cancer, while there is a positive association at the two higher exposure categories. As with Shearer *et al.*, the serum concentration groupings are unevenly distributed which may impact the reported results.

Table 2. Estimated annual and cumulative PFOA serum exposure categories and risk of kidney cancer for Ohio residents assuming 10-year residency and latency (Vieira *et al.* 2013)[17]

Serum Concentration	Concentration Range (µg/L)	No. of Cases	Annual		Cumulative	
			Adjusted OR	95% CI	Adjusted OR	95% CI
No	0	187	Reference			
Low	3.7-12.9	11	0.8	0.4, 1.5	0.8	0.4, 1.5
Medium	12.9-30.7	17	1.2	0.7, 2.0	1.2	0.7, 2.0
High	30.8-109	22	2.0	1.3, 3.2	2.0	1.3, 3.2
Very High	≥110	9	2.0	1.0, 3.9	2.1	1.1, 4.2

[15] Individuals with kidney, liver, pancreatic, and testicular were excluded from the control group.

[16] As OEHHA notes, Vieira *et al.* did not adjust for body mass index which is an identified risk factor for kidney cancer.

[17] Source: Table 2 of Vieira *et al.* 2013 and supplemental material available at https://ehp.niehs.nih.gov/doi/suppl/10.1289/ehp.1205829.

Although Vieira *et al.* estimated PFOA exposure for the OH residents, they did not consider individual residential history and drinking water consumption. These important factors were considered in a follow-up study by Barry *et al.* that followed the Mid-Ohio Valley residents through 2011.

The study by Barry *et al.* was conducted in the same study area as Vieira *et al*. and likely included many of the same participants. It included information from additional years of follow-up and provides a more recent analysis of cancer incidence in the Mid-Ohio River Valley. Barry *et al.* also conducted a more comprehensive assessment of exposure. Moreover, the authors included an analysis of cancer incidence among the workers of the manufacturing facility.

The cohort assembled by Barry *et al.* included 28,541 residents and 3,713 workers who participated in at least one of the follow-up surveys conducted between 2008 and 2011 and for whom an exposure estimate was available. A total of 105 cases of kidney cancer were identified with a complete data set within the cohort – 87 among the residents and 18 among the workers. Barry *et al.* developed estimates of the cumulative PFOA serum concentration using the same model as Vieira *et al.*, but accounted for each participant's reported residential history, drinking water source, tap water consumption, and workplace water consumption.[18] The researchers calculated hazard ratios (HRs) for an increase in kidney cancer among residents, workers, and the combined group cohort for both continuous and quartiles of PFOA serum concentration.[19]

As a result of the additional follow up, refined exposure assessment, and larger cohort size in the analysis by Barry *et al.*, the association between PFOA exposure and risk of kidney cancer is substantially reduced. (**See Table 3.**) Significantly, the hazard ratio is weakest for workers with a significantly higher median estimated exposure.

Animal Carcinogenicity Data

Considering the uncertainty in the epidemiological database, it is important to look at the results of cancer studies in laboratory animals. While several bioassays have been conducted, none have reported an increase in kidney cancer among the exposed animals. Reported cancers have included liver, pancreas, and Leydig cell cancers. The most recent of these studies from the National Toxicology Program (NTP) is reviewed in the PHG draft.[20]

[18] Based on measurements taken in 2005-2006, mean serum concentrations were 0.024 mg/L for community residents and 0.113 mg/L for workers.

[19] The cutoffs for the exposure quartiles are not provided in the publication of supplemental material. The model was adjusted for the same potential confounders as in the analysis by Vieira *et al.*

[20] The NTP study was the key study selected by OEHHA for its 2019 notification level for PFOA.

Table 3. Exposure quartiles and continuous log estimated cumulative PFOA serum concentration and risk of kidney cancer risk with a 10-year lag (Barry *et al.* 2013)[21]

Serum Concentration Quartile	Residents		Workers		Total	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Quartile 1	1.0		1.0		1.0	
Quartile 2	0.94 (0.45, 1.99)	0.02	1.22 (0.28, 5.3)	0.42	0.99 (0.53, 1.85)	0.34
Quartile 3	1.08 (0.52, 2.25)		3.27 (0.76, 14.10)		1.69 (0.93, 3.07)	
Quartile 4	1.50 (0.72, 3.13)		0.99 (0.21, 4.68)		1.43 (0.76, 2.69)	
Continuous	1.11 (0.96, 1.29)	0.17	0.99 (0.67, 1.46)	0.97	1.09 (0.97, 1,21)	0.15

The Animal Data Do Not Support a Public Health Goal Based on Cancer Effects for PFOS

The proposed PHG is based on benchmark dose modeling (BMD) for liver and pancreatic islet cell tumors observed in the chronic animal bioassay performed by Butenhoff *et al.* (2012).[22] The study exposed Sprague-Dawley rats to up to 20 parts per million (ppm) K+PFOS in their diet for 2 years. Carcinogenic effects in the study included tumors in the liver, thyroid, and mammary gland. Pancreatic islet cell carcinomas increased among males, but not females, and the increase was not statistically significant for adenomas or combined adenomas or carcinomas.

The 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 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 other short-term studies, combined with evidence of PPARα and activation of other nuclear receptors,[23] suggests that the liver tumors observed by Butenhoff *et al.*

[21] Source: Barry *et al.* 2013 and supplemental material available at https://ehp.niehs.nih.gov/doi/suppl/10.1289/ehp.1306615.

[22] Butenhoff *et al.* Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. *Toxicol* 293(1-3):1-15 (2012).

[23] 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).

may be of limited relevance to humans. The authors concluded that the liver effects were consistent with activation of peroxisome proliferator-activated receptor alpha (PPARα), constitutive androstane receptor (CAR), and pregnane X receptor (PXR) and that the available human and animal data "do not provide support for cancer risk from exposure to PFOS."

OEHHA's analysis suggests the potential for PFOS to induce hepatic tumors via multiple MOAs in rodents but provides no evidence to support other potential MOAs. The available data show that liver tumors in rats exposed to PFOS are likely caused by the activation of nuclear receptors, such as PPARα, CAR, and PXR.[24] Despite the lack of a dose-response, evidence to suggest the MOA is based on threshold response of nuclear receptors, and the lack of statistical significance, OEHHA develops a CSF based on linear, multiple stage modeling of the combined liver and pancreatic tumors in male rats. Although the available epidemiological and animal toxicity data may suggest a potential concern for carcinogenic effects in humans, the evidence is not sufficient for a stronger conclusion.

Overall, the rodent liver tumors from Butenhoff *et al.* are of questionable human relevance due to potential species-specific mode of action considerations (non-human relevant mechanisms involving xenobiotic nuclear receptors, such as PPARα), the lack of statistically significant increases in hepatocellular or pancreatic carcinomas, and no clear dose response. Moreover, while limited, epidemiological data do not support an association with liver or pancreatic cancer. These data are not strong enough to suggest that PFOS is carcinogenic to humans at low doses.

OEHHA Focuses on the Wrong Non-Cancer Health Effects

OEHHA also presents proposed PHGs for PFOA and PFOS based on reports of non-cancer effects in epidemiology studies. In both cases – liver enzymes for PFOA and total cholesterol for PFOS – the proposed Goals are based on biomarkers for health effects in the absence of evidence of direct effects in the available studies. In addressing this approach in developing toxicity assessments under its Integrated Risk Information System (IRIS), USEPA notes that "[i]f the evidence base primarily includes outcomes or endpoints that are indirect measures (*e.g.*, biomarkers) of the unit of analysis, certainty (for that unit of analysis) is typically decreased" particularly for "findings that have an unclear linkage to an apical or clinical (adverse) outcome."[25] OEHHA has chosen to rely on such indirect measures in developing values for liver toxicity and cardiovascular disease (CVD) for PFOA and PFOS – ignoring the weight of evidence available from human and animals studies.

Although ACC agrees that non-cancer effects are more appropriate basis for the PHGs for PFOA and PFOS, OEHHA has inappropriately selected indirect measures without clear evidence of actual health effects.

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[24] See for example: Elcombe *et al.* 2012.

[25] USEPA. ORD Staff Handbook for Developing IRIS Assessment. EPA/600/R-22/268. Office of Research and Development, Washington, DC (2022). https://www.epa.gov/newsreleases/epa-publishes-iris-handbook-and-final-iris-assessment-perfluorobutanoic-acid-pfba-and

Human Evidence for an Association Between Liver Disease and PFOA is Lacking

EPA's estimate of potential risks of liver effects related to PFOA exposure is based on findings of increased liver enzymes (primarily alanine aminotransferase, or ALT) in epidemiology studies. Although elevation of liver serum biomarkers in humans may be an indication of liver injury, it is not as specific as histological findings or functional tests for liver disease. The reported increase in liver enzymes is small, moreover, and not considered indicative of hepatocellular injury. In analyzing liver enzymes in nearly 50,000 community residents and workers in the C8 Science Panel survey, the Panel noted the while the increase in enzyme levels may suggest small shifts in liver function, they are mainly within the normal physiologic range.[26] Based on its analysis, the Panel concluded that "there was no evidence of a positive association between liver disease and estimated PFOA exposure."

In support of its proposed non-cancer PHG, OEHHA notes that increases in liver weight, histopathology, and biomarkers of liver damage have been observed in laboratory animals, despite the fact that 85 percent of gene expression changes in the livers of mice exposed to PFOA in drinking water were PPARα-dependent.[27] While OEHHA acknowledges that PPARα-mediated liver effects in rodents may have little relevance to humans, the second public review draft includes a new section offering evidence that the hepatotoxicity in rodents is independent of PPARα activation. The section relies primarily on reports of liver effects from studies with PPARα null or knockout (KO) mice. However, care must be taken when interpreting results from studies using PPARα-null or knockout mice in light of the potential for inherent differences between wild-type (WT) and PPARα-null mice that could influence response to chemical exposure.[28] PPARα-null mice have been shown to have defective mitochondrial fatty acid metabolism and to accumulate intracellular lipid droplets in their liver when exposed to hypolipidemic agents, which could make them susceptible to disruption of fatty acid homeostasis.[29] Moreover, PFOA was observed to regulate a set of genes in PPARα-null mice that were not affected by the substance in WT mice with fully functional PPARα.[30]

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[26] C8 Study Panel. Probable Link Evaluation for Liver Diseases (2012). http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Liver_29Oct2012.pdf

[27] Rosen MB *et al.* Toxicogenomic dissection of the perfluorooctanonic acid transcript profile in mouse liver: Evidence of the involvement of nuclear receptors PPAR{alpha}and CAR. *Toxicol Sci* 103(1):46-56 (2008).

[28] Bello SM *et al.* Know Your Model: A knockout does not always make a null. *Lab Animal* 49(3):59-60 (2020).

[29] See for example: Aoyama T *et al.* Altered constitutive expression of fatty acid-metabolizing enzymes in mice lacking the peroxisome proliferator-activated receptor alpha (PPARalpha). *J Biol Chem* 273(10):5678-5684 (1998).

[30] Rosen MB *et al.* PPARalpha-independent transcriptional targets of perfluoroalkyl acids revealed by transcript profiling. *Toxicol* 387:95-107 (2017).

PFOS Exposure Has Not Been Associated with Cardiovascular Disease

Despite a significant number of epidemiology studies investigating the potential association between exposure to PFOS and an increased risk of CVD, the evidence remains equivocal at best. Studies investigating CVD and atherosclerosis "reported mixed or primarily null [negative] results" and those evaluating blood pressure and hypertension "reported no effects or generally mixed associations."[31]

Although there is some evidence for an association with a small increase in total cholesterol and exposure to PFOS, the increase does not correlate with increased CVD. Most recently a recent nested case-control study in Sweden study by Schillemanns *et al.* reported that exposure to five PFAS, including PFOS, although associated with cholesterol levels, "did not associate with an increased risk of myocardial infarction, stroke or their composite endpoint."[32] While this study was published in early 2022, it was not identified by either OEHHA. The lack of an association with CVD led the C8 Science Panel to raise the possibility that people with high cholesterol may retain PFOA, rather than PFOA being responsible for an increase in cholesterol.[33]

Derivation of Public Health Goals for PFOA and PFOS Include Overly Conservative Assumptions

The problems with OEHHA's selection of key studies notwithstanding, ACC has several concerns with the derivation of the draft cancer PHGs for PFOA and PFOS. In both cases, a benchmark response (BMR) of 5 percent is used despite OEHHA guidance that a BMR of 10 percent be used for animal studies and for typical epidemiology studies, although lower effect levels may be appropriate for large epidemiological data sets.[34] While the OEHHA guidance suggests that a lower effect level may be appropriate for large epidemiological data sets, neither the Shearer *et al*. or Vieira *et al*. studies can be considered large. OEHHA provides no rationale for why a lower BMR was chosen.

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[31] USEPA. Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water. Public Comment Draft. EPA Document No. 822P23005. Office of Water (2023), at 4-6. https://www.regulations.gov/docket/EPA-HQ-OW-2022-0114

[32] Schillemans T *et al.* Per- and polyfluoroalkyl substances and risk of myocardial infarction and stroke: a nested case–control study in Sweden. *Environ Health Persp* 130(3):EHP9791 (2022).

[33] Fletcher T *et al.* Probable Link Evaluation for heart disease (including high blood pressure, high cholesterol, coronary artery disease). C8 Science Panel (2012). http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Heart_Disease_29Oct2012.pdf

[34] OEHHA. Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures. Sacramento, CA, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (2009), at 27. OEHHA 2009.

OEHHA also applied a body weight scaling factor to the human equivalent dose (HED) for PFOS,[35] despite using a BMD model and applying a dose adjustment factor (DAF) to account for the difference in serum half-live between humans and the Sprague Dawley rats used in the study by Butenhoff *et al.* OEHHA guidance notes, however, that -

> The basic approach [to benchmark dose methodology] is to fit an arbitrary function to the observed incidence data, and to select a "point of departure" (POD) (benchmark dose) within the range of the observed data. From this a low dose risk estimate or assumed safe level may be obtained by extrapolation, using an assumed function (usually linear) or by application of uncertainty factors. The critical issue here is that no assumptions are made about the nature of the underlying process in fitting the data. The assumptions about the shape of the dose response curve (linear, threshold, etc.) are explicitly confined to the second step of the estimation process, and are chosen on the basis of policy, mechanistic evidence or other supporting considerations. The benchmark chosen is a point at the low end of the observable dose-response curve. . . Because real experimental data include variability in the response of individual subjects, and measurement errors, likelihood methodology is applied in fitting the data. A lower confidence bound (usually 95%) of the effective dose (LED10), rather than its maximum likelihood estimate (MLE), is used as the point of departure. This properly reflects the uncertainty in the estimate, taking a cautious interpretation of highly variable or error-prone data. It also reflects the instability of MLE values from complex curve-fitting routines, which has been recognized as a problem also with the linearized multistage model.[36] (emphasis added)

Since OEHHA uses a linear, low dose extrapolation to calculate the cancer slope factor, there is no need to apply an additional body-weight adjustment.

A Relative Source Contribution of 20 Percent is Not Supported by the Available Information

In calculating the proposed PHGs OEHHA assumes the default relative source contribution (RSC) of 20 percent. In all cases, EPA reasons that the available exposure data for the substance are not sufficient to enable a quantitative characterization of relative exposure sources and routes.[37] On the contrary, there is a large amount of information available to the Agency for these substances that can be used to develop a more appropriate RSC. In fact, a few states have

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[35] According to the draft PHG, OEHHA applied an adjustment of $(BW_{animal}/BW_{human})^{1/8}$ to account for toxicodynamic differences between the species.

[36] OEHHA 2009, at 27.

[37] PHG Draft, at 232, 233.

evaluated the available information for the chemicals and concluded that an RSC of 50 to 60 percent is more appropriate.[38]

There have been several studies of dietary, dust, and inhalation exposure to PFOA and PFOS, none of which suggest that exposures other than drinking water are likely to add up to 80% of the allowable daily intake.[39] Additionally, Garnick *et al.* estimated an "actual RSC" for PFOA and PFOS of 0.95 based on the 95th percentile background exposures for women using data from a 2011 study by Lorber and Egeghy[40] and national serum concentration data from the National Health and Nutrition Examination Survey (NHANES).[41] Correcting the RSC to appropriate data-driven values rather than the default makes a significant difference to the resulting PHG.

As outlined above, data on the carcinogenic potential of PFOA and PFOS are equivocal and should not be the basis of the PHGs. While the Goals are more appropriately based on evidence for non-cancer health effects, OEHHA's focus on biomarkers, in the absence of clear evidence of health effects, is flawed and requires reconsideration.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

Enclosure

[38] These states include Michigan, Minnesota, New Hampshire, New York, Pennsylvania, and Washington State.

[39] Sunderland EM *et al.* A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J Expo Sci Environ Epidemiol* 29(2):131-147 (2019).

[40] Lorber M and Egeghy PP. Simple intake and pharmacokinetic modeling to characterize exposure of Americans to perfluorooctanoic acid, PFOA. *Environ Sci Technol* 45 (19): 8006–8014 (2011). https://doi.org/10.1021/es103718h

[41] Garnick L *et al.* An evaluation of health-based federal and state PFOA drinking water guidelines in the United States. Sci Total Environ 761:144107 (2021).

Recent Publications Not Included in
Second Public Review Draft of Public Health Goals
for PFOA and PFOS in Drinking Water

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