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Pesticide and Environmental Toxicology Branch
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Attention: PHG Program

Re: WSPA Comments Regarding Proposed Public Health Goals for Perfluorootanoic Acid (PFOA) AND Perfluorooctane Sulfonic (PFOS) in Drinking Water

Ms. Hermelinda Jimenez:

Western States Petroleum Association (WSPA) appreciates the opportunity to submit comments on the proposed public health goals (PHGs) for PFOA and PFOS. Based on WSPA's review of the Technical Support Document, WSPA has noted that there are data limitations that were not accounted for in the methodology for developing the PHGs, resulting in outlier proposed PHG levels inconsistent with prior analysis and the work of numerous other agencies. WSPA requests that OEHHA work to address the limitations of the data and to further address those limitations in the methodology used to develop PHGs.

The proposed PHGs in drinking water published by OEHHA are reportedly based on the most sensitive health effects, as follows:

- **Cancer endpoints:** The proposed PHG for PFOA is based on kidney cancer in humans, while the proposed PHG for PFOS is based on liver and pancreatic tumor data from rat studies.
- **Noncancer endpoints:** the most sensitive noncancer endpoints being liver damage for PFOA and clinically relevant increased total cholesterol for PFOS

Table S1. Proposed Public Health Goals and Health-Protective Concentrations

Chemical Name	PHG (ppt)	PHG Effect(s)	HPC (ppt)	HPC Effect
Perfluorooctanoic acid	0.007	Kidney cancer (human data)	3	Increased risk of liver damage (human data)
Perfluorooctane sulfonic acid	1	Cancer (animal data)	2	Increased total cholesterol (human data)

HPC, health-protective concentration; PHG, public health goal; ppt, parts per trillion (equivalent to nanograms per liter or ng/L)

The proposed PHGs and noncancer HPCs are different from the reference levels supporting the notification levels OEHHA recommended to SWRCB in 2019.[1] This is due to a number of factors, including the availability of new studies, the use of human data when possible, and changing toxicokinetic analyses. While new data may be available, the scientific community does not agree on health toxicity values for PFAS, including those for PFOA or PFOS. The PHGs that OEHHA proposed are orders of magnitude lower than what OEHHA previously published and vary drastically from the standards implemented or proposed by other states.[2] Indeed, OEHHA is the first to propose parts-per-quadrillion sensitivity for PFOA. The studies relied upon by OEHHA do not support the proposed PHGs or HPCs.[3]

WSPA provides the following specific comments.

1. **OEHHA Analysis:** Cancer endpoint for PFOA
   - *Dose-response analysis of the human kidney cancer data for the PFOA PHG:* The epidemiologic studies by Shearer *et al.* (2021) and Vieira *et al.* (2013) include data sufficient for quantifying cancer risks. In these two studies, PFOA exposure was assessed using either directly measured serum PFOA levels in each individual (Shearer *et al.*, 2021), which are good indicators of long-term PFOA exposure, or individual PFOA serum levels estimated using a validated exposure model (Vieira *et al.*, 2013). The cancer slope factors derived from these studies are within about six-fold of each other. To make maximum use of both these strong studies, the geometric mean of the cancer slope factors, 0.0026 per ng/kg-day, is used to derive the proposed PHG of 0.007 parts per trillion (ppt) for PFOA.

COMMENTS:

The study by Shearer *et al.* (2021) should not be used to quantify attributed risk of renal cell carcinoma (RCC) to a PFAS-exposed population due to inconsistencies in the methodology,

[1] In 2019, OEHHA developed reference levels of 0.1 ppt for PFOA based on pancreatic and liver tumors in rats and 0.4 ppt for PFOS based on liver tumors in rats. However, the cancer-based reference levels were lower than could be reliably detected in drinking water using currently available technologies. Thus, OEHHA recommended that SWRCB set the notification levels for PFOA and PFOS at the lowest levels that could be reliably detected in drinking water (5.1 ppt for PFOA and 6.5 ppt for PFOS). OEHHA also developed noncancer reference levels of 2 ppt for PFOA based on liver toxicity in mice and 7 ppt for PFOS based on immunotoxicity in mice (OEHHA, 2019).

[2] WSPA notes that US EPA is working toward setting enforceable drinking water limits and suggests that OEHHA could work with US EPA on PHGs and drinking water standards.

[3] Additionally, according to Enthalpy Labs, an accredited national laboratory that specializes in PFAS analysis in waters, the reporting limit for PFOA and PFOS is circa 2 ppt. Thus, reliably and consistently testing for the published PHGs would present a significant analytical challenge. The volume of water required to be able to detect in the low ppt range is already significant (~2L). A decrease of detection limit by more than two orders of magnitude would significantly increase the volume of water required. Further, in the efforts to reduce detection limits, which requires significant preconcentration steps, any trace constituents in the water sample would be magnified analytically. Magnification of trace constituents such as metals or salts may impact instrument performance and sensitivity.

insufficient power within the sample size, and an incomplete outlier analysis. The conclusions made by Shearer *et al.* (2021) cannot rule out bias, multiple comparisons, and random chance as a conclusion.

- Results from Shearer *et al.* (2021), Barry *et al.* (2013), and Viera *et al.* (2013) have inconsistent results across models, and therefore should not be relied upon to set PHGs.
- The study by Shearer *et al.* (2021), did not use appropriate adjustments when conducting comparisons between their samples, which can increase the probability of a type I error, *i.e.*, finding an association when one does not exist. Furthermore, in this study, the sample sizes were very small and did not have a sufficient case to control ratio.
- In Shearer *et al.* (2021), absolute risk of renal cell carcinoma (RCC) was not reported in the exposed population as compared to absolute risk of RCC in the general population. The authors only reported relative risk for the exposed and unexposed groups. This obscures any information on risk of RCC in the unexposed group as compared to the larger population across the United States.
- In Shearer, *et al.* (2021) the authors used a continuous model that was positively skewed without reporting whether they tested for leverage in outliers. Only the highest quartile for exposure was associated with an elevated OR as compared to the lowest quartile. Within the 4th quartile, the range of exposures is highly skewed to the right, meaning that there is a more uneven distribution of exposures than would be expected in a normal distribution. Overall, the average exposure and range is different for each quartile, which is not ideal for drawing conclusions using this type of study.
- In a study with skewed data, outlier testing would typically be conducted. It is not clear whether outlier testing was conducted by Shearer *et al.* (2021). The authors also did not show a distribution of the data so that the reader can see whether or not there is a cluster of exposures to the far right (or left) versus individual outlying data points that may be skewing the overall mean.
- Based on the results from Table 2, it seems that the authors failed to adjust for the effect of other PFAS in their model. For example, in the second column, the authors added a variable to account for the potential effect of all other PFAS in order to be able to evaluate the effect of PFOA alone. However, when the authors added in this additional variable for all other PFAS, the effect for PFOA exposure and RCC was no longer significant. In other words, when other PFAS are adjusted in the model, the relationship for the continuous model is gone, which indicates that an external, unmeasured factor correlating with PFAS exposure may be related to RCC on a causal pathway. Of note, the loss of statistical significance for PFOA and RCC does not necessarily mean that another PFAS chemical is a significant factor in the development of RCC. This finding may indicate that there is simply correlation between PFOA and RCC with another PFAS chemical and would need to be studied separately to draw any conclusions.

- Another point is that the cohort used by Shearer *et al.* (2021) is a cancer screening trial. It is very likely that there is bias between cases and controls, as people are more likely to go to a cancer screening trial if they have some indication that they may be at increased risk for cancer. Furthermore, the authors acknowledged they did not have a diverse set of individuals enrolled in their trial, indicating that this likely obscured any potential racial or ethnic differences in PFAS concentrations and RCC risk.
- There is only a 1:1 ratio between cases and controls, when the ideal ratio is 1:4 cases to controls. This indicates that the paper is underpowered and any conclusions cannot rule out bias, multiple comparisons, and random chance as a conclusion.
- The study by Shearer *et al.* (2021), therefore, cannot be used to reliably quantify the attributed risk of RCC to a PFAS-exposed population.

2. OEHHA Analysis: Non-cancer endpoints for PFOA

- *Human liver toxicity as the basis for the noncancer HPC for PFOA:* The proposed noncancer HPC for PFOA is based on an increased risk of liver toxicity, as indicated by elevated alanine aminotransferase (ALT) levels (Gallo *et al.*, 2012) exceeding clinically based reference levels used by the International Federation of Clinical Chemistry and Laboratory Medicine. The study involved residents of the Mid-Ohio Valley who lived near a chemical plant known to have emitted PFOA into the surrounding environment, and whose ALT increased with increasing serum levels of PFOA. This is the basis of an acceptable daily dose of 0.87 ng/kg-day and a proposed noncancer HPC of 3 ppt for PFOA.

COMMENTS:

Gallo *et al.* (2012)'s reportedly "elevated" ALT levels were actually well below the upper bound for normal ALT reference values reported by the IFCC. Therefore, there is no basis for the calculated acceptable daily dose and proposed noncancer HPC by OEHHA.

- Gallo *et al.* (2012) report comparisons with the liver function values reported in the International Federation of Clinical Chemistry and Laboratory Medicine. However, IFCC's own study provides a range of ALT reference intervals that encompass the values demonstrated by Gallo, *et al.* For example, the 2010 IFCC study by Cerrioti *et al.* (2010) titled, "*Common reference intervals for aspartateaminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) in serum: results from an IFCC multicenter study*" listed in the IFCC reference database, reported RIs for ALT of 8-41 U/L for females and 9-59 U/L) for males, respectively.
- The means reported by Gallo *et al.* (2012) (20.8 ± 16.0 IU/L in women, 31.0 ± 22.5 IU/L in men) were well below the upper bound reference interval provided by the IFCC of 41 U/L for females and 59 U/L for males.
- The means reported by Gallo *et al.* (2012) were well below the upper bound reference interval provided by The Mayo Clinic Laboratory upper bound reference interval of 45

U/L for females and 55 U/L for males. It is recommended that a full statistical analysis, including measures of interindividual variability be conducted to compare the data collected by Gallo *et al.* to published values representing normal healthy individuals.

- The means reported by Gallo *et al.* (2012) were well below the maximum value of 65 U/L (for men and women) reported in a recent review by Drs. Kasarala and Tillmann (2016).

- Overall, the study reporting abnormal elevated concentrations of ALT in a PFOA exposed population is based on inconsistent data for ALT in "normal" populations. The ALT values reported by Gallo *et al.* (2012) fall well within normal ranges according to multiple medical diagnostic sources. .

- In setting these recommendations, OEHHA used uncertainty factors (UF) to calculate the proposed non-cancer PHGs. UFs are used in noncancer risk assessments when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors. This UF methodology is in contrast to the practice used in cancer risk assessment where a surface area or body weight correction from animal to human is made and a 95% confidence interval of the slope of the dose response are typically used.
- OEHHA used a combined standard UF of 300 to account for interspecies extrapolation and intraspecies variability in the calculation of the proposed non-cancer PHG. A report by the US EPA suggests using data-derived extrapolation factors (DDEF) when supported by reliable data and quantitative data, as these are more precise and accurate that the default UF used by OEHHA (USEPA, 2014). This requires availability and adequacy of experimental data and/or reliable model predictions. However, OEHHA only considered the standard UF when calculating their proposed non-cancer PHG.

- OEHHA relied upon a method utilizing numerous uncertainty factors to account for the paucity of usable data to calculate non-cancer PHGs for PFOA and PFOS. We suggest the use of data-derived extrapolation factors instead of uncertainty factors to reduce uncertainty in the already highly uncertain derivations for the PFOA and PFOS PHGs

3. **OEHHA Analysis:** Cancer endpoint for PFOS
   - *PFOS PHG based on cancer endpoint:* OEHHA did not identify any epidemiologic studies of PFOS that could be used for quantifying cancer risk in humans. Thus, the proposed PHG for PFOS is based on cancer data in laboratory animals (Butenhoff *et al.*, 2012). There is not adequate analogy between the development of cancer following PFOS exposure in humans and animals. Calculation of a cancer endpoint for humans is not appropriate in this case.

COMMENTS:

The study by Butenhoff, *et al.* (2012), which was used to assert potential oncogenic effects of PFOS, had critical flaws in methodology. However, OEHHA used these results to calculate a

subsequent cancer slope factor (CSF) despite the lack of a dose-response and non-linear results shown in this study. In their development of a CSF, which assumes linearity, dose-response, analogy, and a plausible MOA, OEHHA did not account for the error and uncertainty in each of these factors. Furthermore, the error associated with each of these factors is compounded exponentially, leading to nonconfidence in derivation of the OEHHA CSF for PFOS.

- The 2021 OEHHA report relied almost solely on an article by Butenhoff, *et al.* (2012) to assert the potential oncogenic effects of PFOS.
- The Butenhoff, *et al.* paper did not report any kind of dose-response for hepatocellular adenomas in male rats with PFOS exposure.[4] In their study, they reported that exposure to a feed concentration of 0.5 or 2 ppm both led to 6% of animals with hepatocellular adenomas, a feed concentration of 5 ppm led to 2% of animals with adenomas, and the highest feed concentration of 20 ppm led to 11% of animals with adenomas. This very clearly illustrates that there is no kind of dose response trend reported in these animals. Furthermore, only the highest exposure group led to a statistically significantly increased incidence of hepatocellular adenomas. The authors later disclosed this dose was at least one order of magnitude higher than the highest reported human serum PFOS concentration.[5]

- However, OEHHA combined the incidences of liver and pancreatic tumors, as reported in Butenhoff, *et al.*, to calculate a Benchmark Dose Level 5% (BMDL05) of 14.7 mg/kg-day. A benchmark dose is a concentration or dose that produces a predefined adverse effect. BMDL05 is the benchmark dose at which 5% of subjects elicited the identified response.

- In their 2021 report, OEHHA indicated that *"[w]hen data are not amenable to BMD modeling, OEHHA uses the…NOAEL…or….LOAEL* (OEHHA, 2021: p. 19). Instances in which BMD modeling would not be appropriate for a data set would be if there is no clear dose-response and/or the data is non-linear, as is the case with the Butenhoff, *et al.* study. OEHHA does not address these inconsistencies.

- Regardless, OEHHA then converted their BMDL05 to a human equivalent dose (HED). Body weight scaling (3/4 weight calculation) was used to account for interspecies differences between humans and rats. However, OEHHA noted in a previous 2009 report that this is not sufficient (OEHHA, 2009). The 2009 report indicated that "*it is often observed that the uptake, metabolism and elimination of the carcinogenic substance…is non-linear, especially at the higher doses employed in experimental animal studies*" and further recommended a non-linear, non-generic extrapolation for these instances (OEHHA 2009: p. 25). This critical flaw is further compounded by subsequent calculation of a CSF, as discussed below.

[4] As the literature is largely inconclusive about the potential carcinogenic effects of PFAS compounds, their carcinogenicity has not yet been established in human or animal models.
[5] There is only limited evidence of a potential association between high PFAS occupational exposure and the development of kidney, liver, or pancreatic cancer.

- OEHHA calculated a human cancer slope factor (CSF) of 15.6 mg/kg-day for PFOS (OEHHA 2021, p. 224-225). The cancer slope factor is a calculation of the cancer risk (proportion affected) per unit of dose (USEPA, 1992).
- However, they failed to acknowledge that Butenhoff *et al.* actually concluded "[*h]uman epidemiological data do not provide support for cancer risk from exposure to PFOS*" (Buttenhoff *et al.* 2012: p. 14). The derivation of a CSF by OEHHA is based on flawed methodology as the data do not support causal association with PFOS exposure in humans.
- The OEHHA's approach with regards to Butenhoff, *et al.* is inconsistent with their previous report, and no explanation is given to address these differences.

4. OEHHA Analysis: Non cancer endpoint for PFOS

- Increased cholesterol in humans as the basis of noncancer PHG for PFOS

COMMENTS:

The current peer-reviewed literature is inconclusive as to a potential association between PFOS exposure and increased serum lipid concentrations. In fact, multiple animal studies show a negative correlative effect (*i.e.,* PFOS exposure decreases serum lipids), including almost half of the studies cited by OEHHA. Therefore, the evidence is insufficient to use increased cholesterol as a critical endpoint for non-cancer PHG for PFOS.

- Per OEHAA regarding the summary of findings for cholesterol modulation in humans following PFOS exposure,
    - "Eight of the 15 studies in adults that reported on PFOS and total cholesterol (TC) or low density lipoprotein (LDL) identified some evidence of a positive association, four found no association including the most recent NHANES study by (Liu *et al.*, 2018b), one reported a negative association, and the others presented results that were difficult to interpret (marked as "U") (Appendix 7, Table A7.12). Only one of the PFOS studies that did not find evidence for a positive association with either TC or LDL reported an association for triglyceride levels. This was the relatively small cross-sectional study by (Yang *et al.*, 2018) (N=145) and the major findings were not statistically significant."
- Nearly 50% (7 out of 15 studies) found either no association or a negative association between PFOS exposure and increased serum lipid concentration, so the studies do not support OEHHA's use of cholesterol as the basis of the HPC. Multiple studies show a negative correlative effect (*i.e.*, PFOS exposure decreased serum lipids), which directly contradicts OEHHA's assertion that there is a causal relationship between PFOS exposure and increased serum lipid levels.
- The lack of association between serum lipids and PFOS exposure is similar to the results of serum lipid and PFOA exposure. Most studies with quantitative estimates of effect levels for cholesterol modulation, defined as the level at which a significant alteration in serum

cholesterol concentration is observed, featured a cross-sectional design, which precluded their use as a basis to draw conclusions about causation. The majority of the studies did not address the requisite criteria for general causation, including the lack of a dose response in humans, the lack of consistency between humans and animals, and the lack of a defined mechanism of adverse effects, as outlined in the Bradford Hill Criteria, or the scientifically established methodological basis for evaluating causality.

- OEHHA reported that metabolism of cholesterol and fatty acids are very different between animals and humans, making it inappropriate to use animal studies to draw conclusions regarding cholesterol levels in humans (OEHHA, 2021).

- Observed PFOS-related cholesterol endpoints in rodents cannot be directly correlated to these same toxicity endpoints in humans due to differences in partitioning of PFOS in organs, methods of administration and ability to enter the blood stream, and the sensitivity of specific receptors thought to be involved in PFOS-altered lipid metabolism, such as peroxisome proliferator-activated receptor-alpha (PPARα). These differences between rodents and humans manifest as contradictory findings across several studies wherein exposure to PFOS was shown to decrease serum cholesterol in both rodents and humans and increase serum cholesterol in others.

- Lastly, the clinical relevance to humans from the findings of rodent studies is unclear due to doses in animal models that are considerably greater than any known to be experienced by humans from environmental exposures.

5. OEHHA Analysis: Assumption that animals and humans are at equal lifetime excess cancer risk at equal lifetime internal doses.

COMMENTS:

PPARα activity has been identified as a potential key mechanism underlying PFOS or PFOA-induced cancer-related outcomes. However, this activity varies significantly between animals and humans. Therefore, *in vitro* or animal studies that hypothesize this mechanism of action should not be relied upon when developing PHGs.

- According to EPA, *in vitro* data can be sufficient to serve as the basis for development of uncertainty factors in humans if the measured response can be linked to an adverse health outcome in humans (USEPA, 2014). In this case, since PPARα activation has been hypothesized to be causative in the development of liver cancer, then results which show PFOS or PFOA can bind and subsequently activate *in vitro* rat and/or human liver preparations would be a sufficient basis to derive non-default adjustment factors for the pharmacodynamic component of UFA (animal to human differences).

- There are well established differences between PPARα activity in animals and humans (ATSDR, 2021). For example, ATSDR recognized that "*Species and compound-related differences in PPARα transactivation by perfluoroalkyls have been demonstrated in vitro" (ATSDR 2021; p. 542).*

- A study by Corton *et al.* (2014) reported that "PPARα activators…are unlikely to induce liver tumors in humans because of toxicodynamic and biological differences in responses [between rodents and humans]" (Corton *et al.*, 2014). In this case, there is ample evidence that humans have far less *PPARα* activity than rats and, thus, the adjustment factor should be calculated accordingly.

- Therefore, it is inappropriate to assume a pharmacodynamic adjustment factor from rat to human (also reported here as a chemical specific adjustment factor, or CSAF) of 1 (meaning equal likelihood of developing the disease from this specific mechanism), as there are known species differences based on results from *in vitro* assays of perfluoroalkyls. Using an adjustment factor of 1 dramatically skews data. However, the OEHHA 2021 report used CSAF of 1 with no explanation.

- One suggestion would be to use the EPA PBPK model published in 2021 instead of the one compartment model for humans used by the EPA to derive the RfD (Bernstein, Kapraun and Schlosser, 2021). The PBPK model will refine the approach to estimate PFOS and PFOA plasma concentrations in humans, which would provide a more sound basis upon which to compare human and rat plasma half-lives.

6. **OEHHA Analysis:** Pharmacokinetic linearity is implied for the development of PFAS-related cancer in human when extrapolating from an animal model.

COMMENT:

Pharmacokinetic linearity was assumed for OEHHA's extrapolation of PFAS-related cancer from animal models to humans. However, this linearity has not been well documented, and multiple studies reported a non-linear dose response.

- Pharmacokinetic linearity is implied but has not been documented. The cancer dose−response is, by default, assumed to be linear.

- Rather, multiple studies support a non-linear dose−response relationship for PFOA and PFOS (Lou *et al.*, 2009), including the Shearer *et al.* (2021) report and other studies relied on by OEHHA.

- Based on the hypothesized mode of action, a nonlinear approach might have been used preferentially for oncogenic response, as the process is thought to involve a cascade of biochemical changes that lead to cell proliferation, processes that are recognized as having a nonlinear response (Tardiff, 2009). As discussed above, OEHHA acknowledged in a 2009 report that non-linear uptake, metabolism, and elimination of potential carcinogens are relatively common, particularly with higher doses used in animal studies (OEHHA, 2009).

- OEHHA should address nonlinearity in the derivation of the CSF instead of relying on a generic, linear approach, as is done in their 2021 report.

Thank you for your continued efforts in this public health goal effort. Should you have any questions or feedback, please contact me at (661) 343-5753 or via e-mail at czimmerman@wspa.org.

Sincerely,

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