DEPARTMENT OF THE NAVY
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Ser N40
October 28, 2021

Ms. Hermelinda Jimenez
PHG Program
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
1515 Clay St., 16th floor
Oakland, California 94612

Dear Ms. Jimenez,

SUBJECT: DEPARTMENT OF DEFENSE COMMENT LETTER – DRAFT TECHNICAL SUPPORT DOCUMENT FOR PROPOSED PUBLIC HEALTH GOALS FOR PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANE SULFONIC ACID (PFOS) IN DRINKING WATER

On behalf of the military Services in California, thank you for the opportunity to comment on the draft technical support document for proposed Public Health Goals (PHGs) for PFOA and PFOS in drinking water, dated July 2021.

The DoD reviewers identified several technical concerns with the proposed drinking water PHGs for PFOA and PFOS, such as the use of a highly conservative uncertainty factor and the lack of a direct correlation with the referenced scientific support in some cases.

The enclosed comments represent consolidated feedback from all of the military Services. Should you have any questions or concerns regarding these comments, please contact Jessica Palmer, Governmental Affairs, at 619-705-5404 or jessica.palmer@navy.mil.

Sincerely,

Jason C Golumbfskie-Jones, P.E.
Deputy Regional Environmental Coordinator
By direction

Enclosure: Department of Defense Comments on the Draft Technical Support Document for Proposed Public Health Goals (PHGs) for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water

Department of Defense Comments on California Proposed Public Health Goals for Perfluorooctanoic Acid and Perfuorooctane Sulfonic Acid in Drinking Water (July 2021 Public Review Draft)

	Organization: Department of Defense	Date Submitted: October 28, 2021

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
Overall	Overall	The proposed California drinking water Public Health Goals (PHGs) of 7 parts per quadrillion (ppq) for PFOA and 1 part per trillion (ppt) for PFOS for cancer endpoints are extremely low due to the use of a highly conservative (300 times) uncertainty factor, are not even able to be detected under available analytical methods, and do not appear to directly correlate with the scientific support referenced in some instances. While the PHGs are not an enforceable drinking water standard (i.e., Maximum Contaminant Level (MCL)), the PHGs are required to be set using the most current principles, practices, and methods used by public health professionals which includes being based on the best available scientifically supportable data . While the public health goal must be based exclusively on public health considerations, public drinking water systems must also identify and report each contaminant detected in drinking water that exceeds the applicable public health goal. The proposed levels, however, are below reliable and available analytical methods, and would not seem to foster the desired public notification endstate.	Please reconsider the scientific support as detailed in our technical comments, feasible detection limits, and consistency with California requirements in establishing drinking water PHGs (e.g., adequate margin of safety).	O
Summary	12	In Barry et al (2013), the authors reported the increased rate of kidney cancer with cumulative log of PFOA concentrations was not significant and did not appear to follow a dose-response trend. This is contrary to the summary of this research paper in the draft PHG, which suggests that there is some dose-response for kidney cancer. In Vieira et al (2013), the authors were only able to show an association between the two highest doses of PFOA and kidney cancer. According to the authors, lower doses did not support a positive dose-response relationship between PFOA and kidney cancer. This is also contrary to the summary of this study in the text of the draft PHG.	Please consider revising the summaries of these studies to address these inconsistencies between the conclusions drawn in the draft PHG and the conclusions made in the referenced sources, particularly the lack of dose-response trends.	S
Summary	13	It would be helpful if the Cancer Slope Factors for PFOA and PFOS were expressed in the same units (by convention: per mg/kg-day).	Recommend that the Office of Environmental Health Hazard Assessment (OEHHA) standardize units in this section.	E
2.4.1	20	For the combined 300 X Uncertainty Factor (UF), the UF for intraspecies toxicokinetic differences is greater than the interspecies. This is a default approach of OEHHA, but is not necessarily the default for other agencies. Given there was interspecies toxicokinetic modelling performed, this is a highly conservative choice.	Please consider providing additional explanation of OEHHA default assumptions and health-protective nature of the UF for intraspecies differences. If there are	S (M)

			data to support the higher uncertainty factor, this should be explained, otherwise a lower interspecies uncertainty factor of 10 would be more appropriate. It should also be explained why the interspecies uncertainty factor was not lowered despite the use of interspecies toxicokinetic modeling.	
2.4.1	19-21	OEHHA generally defaults to use of the linearized multistage model for cancer (aka multistage model in BMDS). For non-cancer, in at least one instance in this assessment, a different model was used (the Hill model is used for ALT, p. 172). OEHHA largely does not consider alternative non-cancer models (which may also be more conservative, e.g., polynomial).	Suggest that OEHHA present the full suite of model parameters and fits from the BMDS tool.	S
4	35	"PFOA and PFOS strongly bioaccumulate in humans and, to a much lesser degree, in animals." The text goes on to demonstrate the differences in humans and animals, but the reader has to decipher this as opposed to the text making it clear. Since animal data is converted to human data in the development of the PHG, it is critical to understand the difference in bioaccumulation in humans and animals.	Please consider adding additional justification of the statement here.	S
4.7	47-48	OEHHA selected the PFOA half-life of 2.7 years based on estimates by the Li et al. 2017e monitoring study of the Ronneby cohort in Sweden. OEHHA provided a range of alternative half-life values and explanations for their choices, and did not automatically default to the most stringent value, which is encouraged. It should be noted that the selected half-life "encompassed values are mostly derived in situations of relatively high PFOA exposure." High and low exposure scenarios may provide different half-life estimates "as exemplified by the findings by Seals et al. (2011) in the C8 Panel participants with lower exposure."	Recommend OEHHA further describe the impacts of half-life determination based on dose/exposure and time in the elimination curve on estimates of clearance.	S
5.1.4	74	If the study does not explicitly state that their personnel were blinded to the results then it is best to not assume that they were.	Please consider deleting the sentence referring to this assumption of blinding.	S
5.2.4	97	The argument presented for the relatively small effects having clinical relevance despite the degree of impact on liver enzymes being lower than those associated with liver disease is not sound. Miller et al., 2009 is cited as supporting the argument of small effects having important impacts on a population, but since it addresses thyroid hormone, cardiac and neurodevelopmental effects, the comparison is not a valid one.	Suggest deleting the Miller et al as a basis for this argument, or more clearly put the degree of impact seen on liver enzymes, possible clinical effects at those levels and lifelong impacts from those effects into context with the lifelong impacts that may arise from impacts to thyroid hormone disruption.	S

5.3.4	104, 106	It is difficult to reconcile OEHHA's conclusion that increased total cholesterol (TC) levels in humans are the most sensitive non-cancer endpoint for PFOS with the following statements from the report: "Eight of the 15 studies in adults that reported on PFOS and total cholesterol (TC) or 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). "A number of large population-based studies in adults with seemingly high quality have reported increases in total cholesterol (US EPA, 2016b; He et al., 2018; Dong et al., 2019). In most, if not all, of these studies serum PFOS levels are highly correlated with serum levels of PFOA or other PFAS. This raises the concern that some of the associations reported in these studies might be due to other PFAS. Because of these high correlations, appropriately adjusting for these other PFAS can be difficult in epidemiologic studies due to issues related to co-variance, and none of the PFOS related studies OEHHA reviewed that identified positive associations with total cholesterol and LDL reported results with these adjustments." Notably, while EPA later indicates (p. 193) that the correlation between PFOA and PFOS are only modest in the Steenland 2009 study (R=0.32), which, while some correlation may not greatly affect overall conclusions of an association, any amount of correlation could skew the estimate of potency made for either of these chemicals individually.	Please consider discussing more thoroughly the uncertainty associated with estimating the specific contribution of PFOA to total cholesterol changes. OEHHA may also consider quantitatively characterizing such changes.	S (M)

5.3.4	106	Regarding cholesterol perhaps the most important issue is that OEHHA rules out potential confounding, reverse causality, and other issues; however, recent re-reviews of the PFOA-cholesterol association have indicated less confidence in this association as being causal. Notably, EFSA (2020[1]) changed their previous conclusions, indicating that new studies and information indicate there is "substantial uncertainty regarding causality" for associations between PFOA (and PFOS) and cholesterol. For example, Donat-Vargas et al. (2019) conducted a longitudinal study of serum cholesterol and PFOA and PFOS; there was no significant association between PFOS or PFOA and serum cholesterol. In addition, the EFSA panel noted that their conclusion hinged on the "postulated biological process around the enterohepatic cycling of both PFASs and bile acids, the latter affecting serum cholesterol levels"; in other words, there is a high potential for confounding due to common intestinal reabsorption of bile salts and PFAS and shared membrane transport pathways. Salihovic et al. (2020) conducted a small study that reported various associations between PFAS and bile salts. With regard to transport proteins, people who have high cholesterol endogenously or via diet tend to have higher levels of liver fatty acid binding protein (L-FABP), a regulator of hepatic lipid metabolism; elevated fatty acid-binding protein is associated with increased risk of cardiovascular disease and metabolic disorders. Studies of L-FABP binding by PFOA in rat cells show 40% inhibition of C11 fatty acid binding to L-FABP (Luebker et al., 2002). In other words, PFOA binds with L-FABP, proteins that play a key role in excretion/reabsorption of PFAS. Thus, increased L-FABP from pre-existing high cholesterol could be the cause of increased PFOA bioaccumulation, rather than PFOA causing increased cholesterol.	Please consider re-evaluating potential confounding/reverse causation in associations between PFOA (and PFOS) and cholesterol.	S
5.7.4 and Appendix 8	159, 469	According to OEHHA's review, five of the 10 Key Characteristics (KC) of Carcinogens had sufficient data for evaluation. For PFOA, KC 2 "Genotoxicity" the evidence is weak, at best, yet the report states: "there is suggestive evidence that PFOA and PFOS are genotoxic, thus a genotoxic MOA for cancer remains plausible." PFOA is not DNA-reactive and thus available mutagenicity assays are consistently null; studies of other genotoxic effects (e.g., DNA damage) show only weak effects. For example, in one study (Eriksen et al., 20102), the increase in reactive oxygen species (ROS) production observed for PFOA in human HepG2 cells was not concentration-dependent and was not sufficient to generate DNA damage detected by alkaline comet assay. Other studies of human cell lines were largely negative for chromosomal aberrations in human lymphocytes, micronuclei in human HepG2 cells, and in vivo micronucleus assays in mice were negative, and in vivo chromosomal aberration studies are mixed (IARC,	Please consider revising the consideration of the mechanistic evidence section to more fully describe and evaluate the available genotoxicity data, rather than relying on a list of KCs.	S

[1] EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel), Schrenk, D., Bignami, M., Bodin, L., Chipman, J. K., Del Mazo, J., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L. R., Leblanc, J. C., Nebbia, C. S., Nielsen, E., Ntzani, E., Petersen, A., Sand, S., Vleminckx, C., Wallace, H., Barregård, L., Ceccatelli, S., Cravedi, J. P., … Schwerdtle, T. (2020). Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA journal. European Food Safety Authority, 18(9), e06223. https://doi.org/10.2903/j.efsa.2020.6223

[2] Eriksen, K. T., Raaschou-Nielsen, O., Sørensen, M., Roursgaard, M., Loft, S., & Møller, P. (2010). Genotoxic potential of the perfluorinated chemicals PFOA, PFOS, PFBS, PFNA and PFHxA in human HepG2 cells. Mutation research, 700(1-2), 39–43. https://doi.org/10.1016/j.mrgentox.2010.04.024

		20183). IARC concluded, "…there is strong evidence that direct genotoxicity is not a mechanism of PFOA carcinogenesis," and that there is moderate evidence that genotoxicity overall is not a mechanism of PFOA carcinogenesis (IARC, 2018). Thorough consideration and discussion of the possible mechanisms of carcinogenicity is also needed to fully integrate the evidence and reach conclusions regarding carcinogenic hazard. Further, for the purposes of dose-response, MOA information is critical; assuming a carcinogenic hazard, one must weigh the MOA evidence to determine whether a linear, no-threshold model, or threshold-based model is appropriate. In the case of PFOA, even assuming carcinogenic hazard, the evidence indicates a threshold dose is highly likely.		
6.1.1	180	OEHHA used increases in liver enzymes (specifically, ALT) as the basis for its non-cancer RfD and PHG for PFOA, based on a cross-sectional study by Gallo et al. (2012), conducted in the C8 cohort. In this study, serum and liver enzymes were measured at the same, single point in time. Gallo et al. (2012) adjusted for socioeconomic status, alcohol consumption, cigarette smoking, body mass index, race, age, and physical activity. However, Gallo et al. (2012) stated "…Self-reported data of lifestyle characteristics being strongly associated with the exposures of interest can hamper a correct adjustment for potential confounders, *which might be of particular relevance given the small magnitude of the observed associations"* [emphasis added]. OEHHA posited that reverse causation was not likely in this study because ALT showed a clear increase by PFOA exposure (i.e., positive trend). However, it still seems plausible that reverse causation may have impacted results. As noted by Darrow et al. (2016[4]), "circulating ALT levels could also plausibly affect storage and excretion of PFOA driving a correlation between measured serum concentrations of PFOA and ALT… even in a prospective study if subtle pharmacokinetic differences between people drive differences in both biomarkers of exposure and liver damage." Similar logic can be applied to PFOS. ALT can be a marker for injury or death of hepatocytes, and has a half-life of 16 to 24 hours. The reference range is 7 to 45 U/L, with 40 U/L often considered the upper limit of normal. In Gallo et al. (2012), the mean ALT level in men was 20.8 U/L and in women, 31 U/L. Interpreting abnormal liver enzymes requires an understanding of the clinical context. A noted by et al., compare "A patient receiving statin therapy who has an ALT of 80 U/L, who is well and requires continued treatment with the statin compared with a patient with end-stage alcohol-related liver disease with an ALT in the normal reference interval at 30 U/L and who may have a life expectancy of weeks" (Newsome et al. 2018[5]). OEHHA also does not fully consider the occupational studies in which ALT was largely either unaltered, or not outside of the clinically acceptable range (Gilliland and Mandel, 1996; Olsen et al., 2000; 2007). There is also little evidence of frank liver disease in	Recommend that OEHHA revisit and expand the biological significance and larger body of evidence for PFOA and liver enzymes.	S (M)

[3] IARC (2018). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 110: Perfluorooctanoic Acid. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono110-01.pdf 2-amino-2-methylpropanol

[4] Darrow, L. A., Groth, A. C., Winquist, A., Shin, H. M., Bartell, S. M., & Steenland, K. (2016). Modeled Perfluorooctanoic Acid (PFOA) Exposure and Liver Function in a Mid-Ohio Valley Community. Environmental health perspectives, 124(8), 1227–1233. https://doi.org/10.1289/ehp.1510391

[5] Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. Gut 2018;67:6-19.

		PFAS-exposed human populations. Steenland et al. (2015) reported a slight trend in increasing non-hepatitis liver disease in DuPont PFOA production workers, but the trend was not significant, nor were there any significant associations in any individual exposure groups (quartiles). Overall, the cross-sectional study by Gallo et al. (2012), while large, has many limitations, not all of which are fully considered by OEHHA. The findings of this study are overemphasized relative to other more relevant studies, such as those conducted in highly exposed production workers.		
6.1.2	185	Regarding immunotoxicity, in discussing the potential reasons for inconsistencies between Abraham et al. (2020) study, which, unlike Grandjean et al. (2012) found no diminished antibody response to diphtheria, influenza, or tetanus vaccines, OEHHA noted that the study "only had cross-sectional analyses, while the Faroe Islands included both cross-sectional and prospective analyses." This dismissal of the study design is directly contradictory to the arguments made in support of the cross-sectional analyses used for liver enzymes and cholesterol changes.	Recommend that OEHHA revise this section and increase consistency across endpoints in their discussion of the validity of cross-sectional studies.	S
6.1.2	190	Increased total cholesterol in the C8 cohort study by Steenland et al. (2009) was ultimately selected by EPA as the critical study/effect for derivation of the PFOS RfD. Because this is a cross-sectional study, both serum PFOS and total cholesterol were collected at only a single point in time. While serum PFOS may have been fairly stable in this population, cholesterol may not have been. Baseline cholesterol is highly variable not only across the general population, but also within a person from day to day. By taking measurements of serum lipids at only one point in time for each participant, we are not able to capture the impact of diet or daily variability for each person. Related to this point, Steenland et al. (2009) adjusted for body mass index (BMI), exercise and smoking, but did not assess the impact of diet, which may be associated with BMI, but remains important as an independent variable (and in fact, Steenland et al. (2009) notes that age, gender, and BMI were the most important predictors of variance in lipids). It is also worth noting that there is very level evidence of an association between PFOA and cardiovascular disease, which adds to the uncertainty regarding the biological significance of slight upward changes in cholesterol.	Recommend OEHHA re-assess the issue of confounding by diet on the TC findings, and the lack of associations between PFOA and frank cardiovascular effects, in the epidemiological studies.	S
6.1.2	200	The epidemiologic studies cited in support of Shearer et al (2021) are not well summarized or appropriately reviewed. The results of Steenland and Woskie (2012) are confounded by the presence of asbestos (significant mesothelioma incidence in the study population). Asbestos is known to cause renal cell carcinoma (RCC). *See: Karami et al. 2011.British Journal of Cancer. 104, 1797 - 1803; Peters et al. 2018. Canadian Journal of Public Health. 109:464- 472; and Pang et al. 2021. Annals of Work Exposures and Health, 2021, 255-265.* This critical confounding of Steenland and Woskie (2012) reported results also confounds the Barry et al (2014) and Vieira et al (2013) studies, which assess kidney cancer in the same subject population. Consequently, three of the four studies used to support the association between PFOA and RCC are confounded by asbestos exposure.	Please consider including some discussion of the potential for asbestos confounding in the PFOA PHG supporting studies	S (M)
6.2.1	205	This section suggests that the incidence of RCC in this study is almost exactly in line with the expected national average. This could lead to an interpretation that the study did not necessarily find that a link between PFOA exposure and an increase RCC. It could also be	Please consider further clarifying this section, particular if its meant to indicate that PFOA exposure	S

		interpreted in such a way that PFOA exposure may be associated with a significant portion of the national average RCC incidence.	may be responsible for a considerable portion of national RCC incidence.	
6.2.1	207	Table 6.2.3 seems to contradict the statement that adjustment for the effects of other PFAS compounds does not significantly effect the RCC-ORs for PFOA. The highest quartile exposure for PFOA loses its statistical significance when making this adjustment. Considering that the cancer slope factor for PFOA is eventually calculated using the unadjusted PFOA RCC-ORs, there needs to be better justification for discounting the PFAS adjustments.	Please consider additional justification for the continued use of the RCC-ORs that are unadjusted for the effects of other PFAS or possibly additional clarification on why the loss of significance would be expected.	S
6.2.1	212	Kidney cancer is the basis for the OEHHA cancer slope factor and cancer PHG for PFOA. OEHHA's evaluation overstates the strength and consistency of the evidence. OEHHA stated that Vieira et al. (2013), Steenland and Woskie (2012), Shearer et al. (2021), and Barry et al. (2013) found statistically significant associations between PFOA exposure and kidney cancer incidence and death. Looking more closely at the results, however, it is notable that the hazard ratio reported by Barry et al (2013) was 1.09 with a 95% CI of 0.97-1.21, indicating a lack of statistical significance. Further, tests for trend by exposure level were also non-significant, both for 10-year lags and no lag. Steenland and Woskie (2012) reported a statistically significant increased risk of kidney cancer mortality in workers in the highest quartile of exposure with a 20 year lag (≥1,819 ppm-years) or 10-year lag (≥2,384 ppm-years); however, there were no kidney cancer deaths and in third quartile despite a positive trend test in the 10-year lag. OEHHA also skims over the in Consonni (2013) retrospective cohort study of tetraflouroethylene producers exposed to PFOA, in which the SMR for kidney/other urinary organ cancer (SMR 1.69, 95% CI: 0.81-3.11) and there was no dose-response relationship. Perhaps most importantly, OEHHA goes to great lengths to "explain" why the Raleigh et al. (2014) retrospective cohort study of occupational exposure to PFOA would have had negative results, in apparent contradiction of the other studies, according to OEHHA. This study found no association between occupational PFOA exposure and kidney cancer incidence or mortality, compared to a working population at another non-PFOA 3M plant in Saint Paul. Some of OEHHA's criticisms are valid, including that there was a small number of cases (6 deaths; 16 incident cases); however, it is a cohort study, which is a stronger design than the other case-control studies. Further, OEHHA's criticisms of the non-PFOA-exposed 3M worker comparison group appear unfounded. While it is true that information on some confounders in these populations, such as smoking, were not available, the age and sex distribution between the Cottage Grove and Saint Paul plants were very similar. The SMRs for mortality between the two plants from cerebrovascular and other related conditions that OEHHA purports make the Saint Paul plant an inappropriate comparison group are not actually substantially different and should not preclude their use as a comparison population. Further, healthy worker effect is not expected to affect cancer outcomes, as cancer does not develop until later in life and thus the worker is not "lost" before detection. It is appreciated that OEHHA's evaluation of confounding, bias, and other aspects of causal inference are clearly outlined with subheadings; however, the integration of the	Recommend that OEHHA revise its discussion of the kidney cancer weight of evidence and re-visit its analysis of the Raleigh et al. (2014) study, which should not be discounted.	S (M)

		evidence (particularly when considering across-study inconsistencies and study design) is lacking, and the full range of findings within and across studies (or lack thereof) is not given sufficient consideration or discussion.		
6.2.1	214	OHHEA reports that another reason why the Raleigh et al. study may have missed an association with PFOA exposure is because of the method of exposure assessment. The Raleigh et al. study estimated air PFOA concentrations using work history records, industrial hygiene monitoring data (205 personal samples and 659 area samples), information from current and former workers and industrial hygiene professionals, and average annual PFOA production levels. In contrast, the Shearer et al. study measured PFOA levels in human blood of the exposed population. While such blood sample analyses are often taken as a surrogate of PFOA exposure because of PFOA's long half-life in the human body, they only represent a single snapshot in time (a limitation identified by Shearer et al). OHHEA presents no evidence that the Raleigh et al. study exposure estimates are in any way in error or subject to significant uncertainty, but simply concludes that the Raleigh et al. studies estimate of exposure is suspect. Raleigh et al. reports on prior measures of serum PFOA within a fraction of the study population, validating their exposure estimate as similar to previous cross-sectional biomonitoring surveys of this occupational population - indicating indirect occupational exposure at the site.	While such estimates are clearly less useful than blood measures, OHHEA may consider specifying how such estimates are likely to be in error and inappropriate for use in the Raleigh et al study.	S
		The paper by Raleigh et al (2014), which shows no apparent association between PFOA and kidney cancer in 4,668 PFOA production workers compared to 4,359 referent workers, is discounted (not considered useful in adverse effect selection) by OHHEA for a variety of reasons. One reason given by OHHEA is the small number of kidney deaths in the study population (n=6), an effect that might be taken as evidence for lack of effect. OHHEA compares the HR for kidney cancer associated with the highest quartile (n=4) in the Raleigh et al. study with the standardized mortality ratio (SMR) for kidney cancer associated with the highest quartile in the Steenland and Woskie study (n=8), which as noted earlier is confounded by asbestos. Such a comparison is not appropriate as the HR and SMR are different measures. An appropriate comparison of the two study SMRs looks very different. If we look at the PFOA exposed populations in both studies, the Raleigh et al. study SMR for kidney cancer is 0.53 with a 95th CI of 0.20 to 1.16 (n=6), a narrow window around a low mean. In contrast, the SMR for kidney cancer identified in the Steenland and Woskie study is 1.28 with a 95th CI of 0.66 to 2.24 (n=12), a much larger window around the mean. If we follow the logic of OHHEA concerning the width of the 95th CI, then we would conclude that the Steenland and Woskie study demonstrates imprecision. Additionally, a comparison of the SMR from the Steenland and Woskie study exposed population to the SMR for the Raleigh et al. referent (un-exposed) population look very similar. The referent population in Raleigh et al. has an SMR of 1.23 and a 95th CI of 0.73 to 1.95 (n=18) while the Steenland and Woskie study reported an SMR of 1.28 with a 95th CI of 0.66 to 2.24 (n=12). The 95th CIs for these studies suggests, according to OHHEA logic that the Raleigh et al. study is more precise. This comparison could support a finding that the PFOA exposed population of the Steenland and Woskie study has no	Please consider revising the assessments herein of the Steenland and Woskie study and the Raleigh to better compare the precision of both studies, preferably using more direct and applicable comparisons.	S

		greater incidence of kidney cancer than an unexposed population in the Raleigh et al. study.		
6.2.1	218	The statement "Since the incidence of kidney cancer is relatively low" contradicts the statement (p.201) "Kidney cancer is among the top ten cancers diagnosed in the US each year (ACS, 2020a)."	Please revise this statement.	S
6.2.1	219	In its derivation, the CSF for PFOA is directly proportional to the baseline risk (Ro) for kidney cancer (Equation 7). The value (0.02) which represents the baseline risk for the male U.S. population was used. The female baseline risk is half (0.01) the male rate. The report goes on to state, appropriately, that the baseline kidney cancer rate is likely an overestimate given the background exposure of PFOA in the U.S. population. Given this issue, potential bias could be reduced by using the mean baseline kidney cancer rate for both males and females (0.015). Further, based on the OEHHA CSFs, PFOS is 140-fold less potent of a carcinogen than PFOA, which is unexpected given that while both chemicals C8s, when toxicity does diverge, the general toxicological finding that PFOS is more potent than PFOA.	Please consider using combined male/female baseline cancer risk values.	S
6.2.8	222	In the OEHAA PHG, OEHHA states that "the BMR is typically set at 5% above the background or the response of the control group for dichotomous data" (p.19). However, USEPA BMDS guidance states that a BMR of 10% should be used for dichotomous data, but the BMR can be adjusted to account for sensitivity in the evaluated assays. In order to evaluate the sensitivity of the selected CSF to changes in BMR, we re-modeled the selected dataset (Butenhoff et al., 2012b; male hepatocellular adenoma and pancreatic islet cell carcinoma; see Table 5.7.7, p. 150) with a BMR of 10% instead of 5%. Because the selected model (Multistage, Polynomial 1; see Table 6.2.8, p.222) is essentially equivalent to a linear model, the BMDL from the 10% BMR models was approximately 2 times higher than the BMDL of the 5% model. After adjusting for human clearance, TK, and calculating a human equivalent dose (HED), the resulting slope factors from models with 10% BMR were approximately 3% lower than those with a BMR of 5% (note: CSF = BMR/BMDL). Although the difference is small, this allows for some refinement of the CSF and corresponding risk estimates. The largest determining factor for CSF selection is the use of the combined tumor model (part of the USEPA BMDS suite) in lieu of individual tumor models. This method allows for statistical combination of independent tumor types from the same bioassay; the liver and pancreatic tumors are expected to be independent based on MOA understanding. However, the resulting BMDL for the combined tumors models are markedly lower than those from the individual assays. Historically, guidance has recommended evaluation of models beyond the multistage model (including those with non-linear dose response shapes) and selection of the most sensitive POD from the best-fit models of individual tumors.	Please further explore using a BMR of 10% and also consider the appropriateness of the combined tumor model for POD selection.	S
7.1.1	225	Use of the most conservative RSC (20%) with a high-end (95th percentile) estimate of water ingestion (0.053 L/kg-day) has a multiplicative effect on driving down the non-cancer health protective drinking water concentration for PFOA. The same could be said	Please consider whether an alternative RSC would be	S

		of PFOS. Several states have used alternative RSCs (Minnesota uses a RSC of 50% and ATSDR effectively applies a RSC of 100% for water) to account for a larger portion of the exposure "allowance" to arise from water, relative to food, given that water is the primary source of PFAS exposure for those with contaminated drinking water. PFAS exposures from food are quite low, particularly for PFOA and PFOS after phase-out.	appropriate for the PHG derivations.	
8	225	As noted in the comment above, OEHHA employed a high-end water consumption rate to "capture the continued trend of increased water consumption both nationwide and in California." Would it not be appropriate to consider the same reasoning for using a less restrictive RSC that allows for a higher contribution of PFAS from water, given the "continued trend" of decreased production, use, and serum levels of PFOA/PFOS "both nationwide and in California?"	Given the use of high-end water consumption rates, OEHHA may consider increasing the RSC to include a higher proportion of exposure attributable to water sources of PFOA/PFOS.	S
8	228	There appears to be an intrinsic inconsistency in this statement: "OEHHA evaluated US EPA's recently updated water consumption rates published in the Exposure Factors Handbook (US EPA, 2019). While US EPA's updated water intake rates are based on newer data (NHANES, 2005-2010) than those used by OEHHA (CSFII, 1994-1996, 1998), they do not capture the continued trend of increased water consumption both nationwide and in California." OEHHA applies a drinking water intake value of 0.053 L/kg/day (about 4 L/day assuming 80 kg body weight), which is much higher than other agencies. EPA's and EFSA generally apply an intake of 2 L/day. While it is reasonable that people in warmer climates may have higher consumption rates, 4 L/day appears very high relative to other agency approaches and empirical data (e.g., see Vieux et al., 2020[6]).	OEHHA may consider the appropriateness of its water consumption rate and if maintaining this value, provide more discussion of why OEHHA's values are appropriate.	S
Appendix 12	628	The language in the final paragraph on this page is somewhat confusing and requires some kind of clarification. The implication is possibly that more than one case of RCC could come from the same person, or that the exact number of people in each exposure category is not known. In either case, a further explanation of how estimations of these numbers would artificially elevate the BMDL, and why this estimation is not acceptable when other estimations are (estimation of dose using midpoint of range, use of PFOA ORs unadjusted for other PFAS).	Please consider revising the text for additional clarity and explanation of the extent of artificial BMDL elevation.	S

[6] Vieux, F., Maillot, M., Rehm, C.D. *et al.* Trends in tap and bottled water consumption among children and adults in the United States: analyses of NHANES 2011–16 data. *Nutr J* **19**, 10 (2020). https://doi.org/10.1186/s12937-020-0523-6