OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Responses to Peer Review and Public Comments

Technical Support Document: Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water

March 2024

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Responses to Peer Review and Public Comments on Technical Support Document: Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water

Prepared by

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

March 2024

CONTENTS

INTRODUCTION 1
RESPONSES TO EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS 2
DR. JOHN ADGATE 5
DR. HINDRIK BOUWMAN 13
DR. VAIA LIDA CHATZI 17
DR. JAMIE DEWITT 43
DR. JENNIFER SCHLEZINGER 47
DR. ROBYN TANGUAY 66
RESPONSES TO COMMENTS MADE DURING THE FIRST PUBLIC COMMENT PERIOD (July 30 – October 28, 2021) 72
3M COMPANY 73
ASSOCIATION OF CALIFORNIA WATER AGENCIES 107
CALIFORNIA-NEVADA SECTION OF THE AMERICAN WATER WORKS ASSOCIATION 109
THE AMERICAN CHEMISTRY COUNCIL (ACC) ET AL. 111
CALIFORNIA ASSOCIATION OF MUTUAL WATER COMPANIES 132
CALIFORNIA ASSOCIATION OF SANITATION AGENCIES 134
CALIFORNIA COUNCIL FOR ENVIRONMENTAL AND ECONOMIC BALANCE 149
CLEANEARTH4KIDS.ORG 151
COMMUNITY WATER SYSTEMS ALLIANCE 152
US DEPARTMENT OF NAVY 154
ENVIRONMENTAL WORKING GROUP et al. 172
NATIONAL ASSOCIATION FOR SURFACE FINISHING 176
ORANGE COUNTY WATER DISTRICT 177
PFAS REGULATORY COALTION 179
SAN GABRIEL VALLEY WATER ASSOCIATION 185
SILENT SPRING INSTITUTE 187
WESTERN STATES PETROLEUM ASSOCIATION 191
ANONYMOUS AND M MCANEAR 203
RESPONSES TO COMMENTS MADE DURING THE SECOND PUBLIC COMMENT PERIOD (July 14 – August 29, 2023) 207
THE AMERICAN CHEMISTRY COUNCIL 208
ELSINORE VALLEY MUNICIPAL WATER DISTRICT 227

EASTERN MUNICIPAL WATER DISTRICT 230
ORANGE COUNTY WATER DISTRICT 231
SAN JOAQUIN VALLEY DEMOCRATIC CLUB 233
NATURAL RESOURCES DEFENCE COUNCIL et al. 234
MONARCH ACTION 239
REFERENCES CITED IN RESPONSES 242

INTRODUCTION

This document contains responses to public comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the Public Health Goal (PHG) technical support document for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) during the first and second public comment periods, and to comments from the external scientific peer reviewers.

OEHHA released the first draft of this PHG document for public comment on July 30, 2021, and held a public workshop on September 28, 2021 via webcast. The public comment period closed on October 28, 2021. OEHHA received comments from multiple stakeholders.

Pursuant to Health and Safety Code section 116365(c)(3)(D), OEHHA submitted the PFOA and PFOS PHG document for scientific peer review following the closure of the first comment period. Comments were received from the peer reviewers in February 2022.

The external scientific peer reviewers were:

1. John Adgate, Ph.D., MSPH
Department of Environmental and Occupational Health
Colorado School of Public Health
University of Colorado Anschutz Public Health Campus

2. Hindrik (Henk) Bouwman, Ph.D.
School of Biological Sciences
North-West University
South Africa

3. Vaia Lida Chatzi, Ph.D.
Professor of Population and Public Health Sciences
Keck School of Medicine
Health Sciences Campus, Los Angeles
University of Southern California

4. Jamie DeWitt, Ph.D., DABT
Department of Pharmacology & Toxicology
Brody School of Medicine
East Carolina University

5. Jennifer Schlezinger, Ph.D.
Department of Environmental Health
Boston University School of Public Health

6. Robyn Tanguay, Ph.D.
Department of Environmental and Molecular Toxicology
The Sinnhuber Aquatic Research Laboratory
Oregon State University

OEHHA made changes in response to the public and peer review comments as appropriate, and incorporated them into the PHG technical support document, which was released for a

second public comment period from July 14 to August 29, 2023. Revisions were made, as appropriate, to the technical support document in response to comments received in the second comment period. The public comments and peer review comment letters received are posted on the OEHHA website along with this response document, and the final version of the PHG technical support document.

In this document, comments appear in quotation marks where they are directly quoted from the submission. Note that for the public comments where the commenter included a footnote, OEHHA did not copy the footnote into the response document. Footnotes can be seen in the original public comment letters posted on the OEHHA website. Comments calling for non-substantive changes such as punctuation and grammatical corrections have been addressed and are not included in this document.

For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA web site at www.oehha.ca.gov.

OEHHA may also be contacted at:

Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010
Attention: PHG Program

PHG.Program@oehha.ca.gov

(916) 324-7572

Abbreviations:

ALT, alanine aminotransferase

APFO, ammonium perfluorooctanoate

BMI, body mass index

EFSA, European Food Safety Authority

eGFR, estimated glomerular filtration rate

GFR, glomerular filtration rate

HDL, high-density lipoprotein

HPC, health-protective concentration

HR, hazard ratio

LDL, low-density lipoprotein

NHANES, National Health and Nutrition Examination Survey

PHG, public health goal

RCC, renal cell carcinoma

SMR, standardized mortality ratio

TC, total cholesterol

TFE, tetrafluoroethylene

RESPONSES TO EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS

DR. JOHN ADGATE

Comment 1: "Based on my review I have determined that the CalEPA organization's assumptions, findings, and conclusions, including the scientific material from the peer reviewed scientific literature and other authoritative sources, rely on materials that are based on sound scientific knowledge, methods, and practices. The overall write up and the methods employed are based on sound science and the methods and approaches used are defensible. Thus their use in cancer and noncancer health risk assessment also defensible."

Response 1: OEHHA acknowledges the comment.

Comment 2: "The overall draft is well written, with the major assumptions clearly identified and rationale clear in most places. There are instances where the presentation could be improved by more explicit promulgation and/or presentation of the range of uncertainties present in both the underlying data and modeling approaches applied to those data. Some of this is in the summary tables, for example, the ones presenting the range of PODs [points of departure] using different modeling data sets and approaches, but this general approach should be extended to show how these uncertainties address the final endpoints, e.g., PHGs and HPCs. My judgment is that relatively minor improvements in the presentation and interpretation of the human and animal studies will improve the clarity, transparency, and scientific rigor of the document."

Response 2: In response to this comment, OEHHA made improvements in the presentation of the human studies. For example, cancer slope factors for kidney cancer in humans (for PFOA), calculated using upper and lower bounds of the regression slope, were added to Table 6.2.7. Changes were also made for animal toxicity tables to increase clarity. For example, a column for serum concentrations of PFOA was added to Table 5.4.2 (thyroid toxicity from subacute and chronic studies in rats).

Comment 3: "A second issue of note is that much of the analysis of human and animal data seems over concerned with p-values, particularly in epidemiologic studies, an approach that the epidemiology research community is moving away from in favor of reporting all findings, uncertainty bands, and trends (see, for example, Savitz, DA, 2013 and related publications on this topic). Similarly, the analysis of animal studies in also focused on counting the number of studies with positive findings, which is only meaningful if the total number of studies with and without positive findings for each endpoint are also enumerated and then summarized while considering their overall findings in the larger scientific context. So while the approach taken is defensible, the document could be improved by summarizing what is already a comprehensive accounting of the existing literature and more clearly summarizing how, for example, the endpoint analysis from animal studies does or does not contribute to overall weight of evidence findings of the cancer or noncancer endpoints for both PFOA and PFOS."

Response 3: The PHG document includes some discussion of statistical significance (e.g., p-values, confidence intervals, and related statistics). These metrics are important because they provide an estimate of the probability that findings are due to chance. This is a key element of causal inference (Hill, 1965). However, OEHHA agrees that causal inference should not be entirely reliant on these statistical tests. As such, none of the conclusions was based on p-values or on a simple counting of "positive" studies. Rather, OEHHA based its study quality and causal inference evaluations on a large number of factors, including examinations of selection bias, exposure misclassification, outcome misclassification, confounding, effect size, dose-response, and at least a dozen other study quality and causal criteria. These criteria were discussed in detail in Appendix 7. They are also discussed in numerous places throughout the document. For example, see the discussions of these issues for studies of vaccine response (Section 5.1), liver toxicity (Sections 5.2 and 6.1.1), lipid homeostasis (Section 5.3 and 6.1.2), and cancer (Section 6.2.1).

Given all of this, OEHHA acknowledges the importance of the information on causal inference, and has now moved this information from the Appendix 7 into the main portion of the draft PHG document (Section 2.2.2). This section has also been expanded to improve clarity and completeness. Presenting this information early in the document will help emphasize and reinforce the fact that OEHHA has used a wide main range of different factors, and not just statistical significance, to judge study quality. In addition, new wording has now been added to several places in the document emphasizing the fact that a large number of study quality and causal inference criteria were used. With regards to "uncertainty bands," 95% confidence intervals (CIs) are given for all the major study results used to develop the health-protective concentrations. For example, 95% confidence intervals (CIs) for the odds ratio (ORs) reported in the Shearer et al. (2021) and Vieira et al. (2013) used in the cancer slope factor calculations for PFOA are given in Table 6.2.6, and the 95% CIs for the ORs reported in the Steenland et al. (2009) study used for the noncancer health-protective concentration calculations for PFOS are shown in Table 6.1.13. Finally, mention is now made in the draft PHG document, where appropriate, that none of OEHHA's conclusions was solely based on p-values.

Comment 4: "In my judgment the overall the approach to updating previous authoritative review documents from the USEPA and ATSDR is reasonable and, despite my concerns described in the last paragraph [Comment 3 above], the report authors do a good job indicating where additional information has been found and incorporated into their summary. I will note that sometimes the human and animal data tables do not stand alone as clearly interpretable units that are well integrated into the surrounding text. These should be examined for consistency of message, units and footnotes consistency, etc."

Response 4: OEHHA acknowledges the comment. The tables and text were examined for consistency and corrected when it was deemed necessary.

Comment 5: Regarding cancer epidemiology for PFOA, "The proposed PHG and HPC are consistent with the underlying science and the accompanying analysis (see comments on study selection/quality below)."

Response 5: OEHHA acknowledges the comment.

Comment 6: "This scientific presentation could be improved by providing uncertainty bands around the cancer potency estimates. This is especially important for the PHG of 0.007 ppt, a level that is orders of magnitude lower than current best practice detection limits for PFOA in water and other environmental media, but could be done for the HPC (and PFOS slope factor) as well."

Response 6: The 95% CIs on the linear regression slopes for both the Shearer et al. (2021) and Vieira et al. (2013) studies used to calculate the cancer slope factor (CSF) for PFOA were already provided in Table 6.2.7. However, in response to this comment, they are also now provided in the text of the document. In addition, CSFs calculated from these 95% CIs are now also provided (Table 6.2.7). These CIs may provide some indication of statistical "uncertainty" for these particular results. Other, usually more important, aspects of potential uncertainty include issues of bias, confounding, or other errors in the underlying studies, and these are discussed in detail in Section 6.2.1.

Comment 7: Regarding environmental epidemiology for PFOA and PFOS, "This section uses a systematic approach to identifying and critiquing studies, with a focus on the important potential confounders and other scientific issues (e.g., co-occurrence of other PFAS) and their potential effect on the overall analysis."

Response 7: OEHHA acknowledges the comment.

Comment 8: "The weight of evidence determination for the studies to use for the PFOA/kidney cancer determination is reasonable and based on high quality studies with a large number of participants."

Response 8: OEHHA acknowledges the comment.

Comment 9: "Use of the geometric mean for cancer potency is reasonable, per my summary comment above, presenting the range of estimates is also important to make clear the relationship between this finding and the uncertainty around the PHG."

Response 9: OEHHA acknowledges the comment. Please see the response to Comment 6 from this reviewer regarding uncertainty.

Comment 10: "The use of California specific drinking water rates is a defensible choice that is clearly articulated."

Response 10: OEHHA acknowledges the comment.

Comment 11: "Continued use of the default RSC is justified based on the lack of any other compelling data."

Response 11: OEHHA acknowledges the comment.

Comment 12: "The toxicokinetic modeling approach is reasonable: further characterizing the impact of uncertainties (particularly relative to other sources of uncertainty) is important for transparency."

Response 12: OEHHA acknowledges the comment.

Comment 13: "The final risk characterization section is brief but has the essential elements."

Response 13: OEHHA acknowledges the comment.

Comment 14: "I concur that serum/plasma is the "least uncertain" approach to compare to toxicokinetic model outputs."

Response 14: OEHHA acknowledges the comment.

Comment 15: "The comparison to other State standards/health guidance levels is important, incorporating uncertainty bands around the PHG for PFOA in particular, will improve transparency and provide context for what the State of CA is proposing, though it would be useful to repeat that the typical detection limits in water are in the range or, for the PFOA, well above the PHG."

Response 15: OEHHA acknowledges the comment. Comparison to other state and federal drinking water regulations and advisory levels is included in Table 8.1. By statute, the PHG is defined to be a single value, and not a range. To provide an indication of some of the uncertainty in its derivation, OEHHA provided confidence intervals for the cancer slope factors.

Comment 16: "On page 228 a more detailed explanation of why OEHHA's clearance factors differ from the USEPA's should be provided here."

Response 16: More detail has been added in response to this comment.

Comment 17: "Page 27: Note that the description of the Beesoon et al 2012 study is confusing 'indoor air concentrations in the dust samples' makes little sense—if it's PFAS adsorbed to particulate matter measured in indoor air say that; if it's PFAS concentrations measured in house dust that's a different environmental media."

Response 17: The description of the Beesoon et al. (2012) study has been corrected in response to this comment.

Comment 18: "Page 31: Human exposure paragraphs: the text does note that the major route of exposure in the general population is typically food, which is correct, but should also tell the reader that for many of the studies in highly exposed human populations are due to water contamination (e.g., the C8 studies, Ronneby, etc.) in which food, indoor air, dust, precursors are a relatively small contributors to overall exposure in those populations. While you do cite the Vestergren and Cousins (2009) paper on PFOA concentrations in water, the more salient point for this document is that the studies done in high drinking water exposure human populations are the scientific basis for standards/health guidance in most states and California's PHGs for PFOA/PFOS, and there are uncertainties inherent in translating findings from this context [to] populations with more typical exposure profiles."

Response 18: The section to which the comment refers (Section 3.2, *Human Exposure*) already contains a paragraph that starts with: "Contaminated drinking water can also become the main source of exposure" and proceeds to list all the studies of highly exposed human populations, in which this was the case. Additionally, OEHHA considered this when determining the relative source contribution (RSC). When drinking water is the predominant source of PFOA and PFOS, it is justified to use a high (≥50%) RSC to indicate that other exposure sources are relatively modest. However, for California, it is not evident that drinking water is the predominant source, and thus a lower RSC value (20%) was employed. While there are uncertainties when extrapolating from high-exposure populations to low-exposure populations, in the absence of specific data indicating otherwise, OEHHA assumes the relationship is linear.

Comment 19: "Pages 35-40: suggest that you avoid the use of "applied dose" as it is a vague concept. Wherever you can use either administered or internal dose."

Response 19: In response to this comment, all instances of "applied dose" have been changed to "administered dose."

Comment 20: "Page 40: 'Clearance factor' (CF is used later in the document) important in this document. It's important for conversions but it's not in the table of acronyms at the beginning. Furthermore, the units in Table 4.5.1 are unclear (and not consistent with the Summary) and there are unstated assumptions on the conversation of PFAS volume to mass. In general this issue is much more clearly explained in the section on ADIs and related calculations on pages 182 and 197."

Response 20: CL (clearance) is in the list of abbreviations. In response to this comment, the "CF" abbreviation that occurred later in the document has been changed to CL, and the role of clearance in relation to acceptable daily dose calculations (along with appropriate unit definitions) was added to the beginning of Chapter 4. Table 4.5.1 presents published values specifically for renal clearance, which are expressed in mg/kg-day, and not for overall (plasma) clearance, expressed in units of L/kg-day, that was used for the PHG calculation and is included in the Summary. Thus, the values in Table 4.5.1 would not be directly compared to CL values in the Summary. Clearance

units in Table 4.5.1 (ml/kg-day) are chosen to simplify presentation. Expressing everything in L/kg-day would result in significantly increased page space of the table without a clear benefit to presentation.

Comment 21: "Page 65: The write up here is too focused on statistical significance and does not reflect best practice in the interpretation of epidemiological studies. A more nuanced presentation will look at both direction and trend in all the endpoints is warranted here: see Savitz reference and related papers in the literature."

Response 21: Although OEHHA's conclusions were based on a large number of study quality and causal inference factors (please see the response to Comment 3 from this reviewer), OEHHA agrees that this part of the draft PHG document could be considered "too focused on statistical significance." In response to the comment, the text has been edited to note that Tables A7.3 and A7.4 include data on the factors OEHHA used to evaluate study quality and causal inference, and that statistical significance was not the only criterion used (Section 5.1.1 of the draft PHG document). It should also be noted that confounding, selection bias, exposure misclassification, reverse causality, biologic plausibility, and several of the other quality and causal criteria used to evaluate the studies of immunotoxicity are discussed at length in Section 5.1.1 of the PHG document.

Comment 22: "Page 66: Noting the sample size in the text here, i.e., the N for the vaccine response studies in this section, is important and places in context the important observation that the BMDL is 6-13 fold lower than the lowest "dose" in these studies."

Response 22: The exact number of children included in each set of the analyses is not clearly stated in the study. However, OEHHA agrees with this comment and has now provided a rough estimate based on the somewhat limited information provided in the publication (Section 5.1.1, where the Budtz-Jorgensen and Grandjean (2018) study is described).

Comment 23: "Page 95: Table 5.[2.4] is very important and would be it would be better if it did not break across pages so the reader can compare the human and animal data on PFOA and PFOS and liver toxicity."

Response 23: In response to this comment, Table 5.2.4 has been formatted to no longer break across the page.

Comment 24: "Page 96: The text at the top of the page here probably belongs in the lipids section and not before it."

Response 24: In response to this comment, the paragraph immediately preceding Section 5.3 has been moved to the top of Section 5.3 (*Perturbation of Lipid Homeostasis*).

Comment 25: "Page 104: Again, counting studies versus and a more nuanced presentation is not the most defensible scientific approach. The qualitative scoring needs to be explained more clearly in the main text as it refers to an appendix here."

Response 25: Please see response to Comment 3 from this reviewer. The discussion of the criteria used to judge study quality and causal inference has now been moved out of the appendix and into the beginning of the main document.

Comment 26: "Page 105: There is more recent data particularly in humans on half-lives particularly in highly exposed communities. While some of these studies are small, they show shorter half-lives (at least in highly exposed communities) though there's a considerable variance between people. My point here is that the half live number cited from the Olsen study may not reflect what is observed in these high exposure communities; what that means for more typical serum levels found in the general population should be addressed somewhere here."

Response 26: As seen from Tables 4.7.1 and 4.7.2 in the draft PHG document, half-life estimates for PFOA and PFOS from Olsen et al. (2007) are a bit higher than those chosen by OEHHA. However, all these half-life estimates are long (in the order of years) and choosing one or another would not make much difference in almost any epidemiologic study. Furthermore, if exposures (or serum levels) change over time, any resulting bias would most likely be towards finding no association, not towards the associations that were seen. There are some exceptions to this, but they are incredibly rare. To address the comment, however, the reference to Olsen et al. (2007) was replaced by the reference to Tables 4.7.1 and 4.7.2, which show a range of studies encompassing both the general and highly exposed populations.

Comment 27: Referring to Chapter 6 (*Dose-Response Assessment),* "The general approach used here is scientifically justified, though having uncertainty bands would help in illustrate the uncertainties. Also, consider comparing various approaches for dose response and give the reader confidence that the various approaches provide evidence of consistency independent of the model chosen."

Response 27: While OEHHA does not provide uncertainty bands, it provides and applies the BMD:BMDL ratio as one metric of model suitability and to show uncertainty. Thus, several modeling results in Chapter 6 were rejected based on the large BMD:BMDL ratio.

As for comparing various approaches for analyzing dose-response, as indicated in OEHHA's guidelines (OEHHA, 2008, 2009), the use of BMD modeling is the default approach for the analysis of animal data. This practice is also consistent with the US Environmental Protection Agency's (US EPA) practice and guidelines for risk assessment. While other approaches to BMD modeling exist, OEHHA does not expect significant differences with the BMDS results as other comparable platforms have similar build and capabilities. Nonetheless, OEHHA is currently exploring alternative dose-response modeling platforms for suitability in risk assessment.

Comment 28: "Page 182: the explanation/use of the PFOA clearance factor here is much clearer than earlier text."

Response 28: In response to this comment, a similar definition of clearance has been added to the beginning of Chapter 4 (*Toxicokinetics*).

Comment 29: "Page 184: The animal section here is not terribly helpful given the decision to use human data; there should at least be an explicit statement what, if anything, the animal data adds. In contrast, the PFOS human studies analysis is clear and justified."

Response 29: In the spirit of due diligence, it is OEHHA's practice to evaluate both human and animal studies, and to present candidate critical endpoints and PODs from both study types, when possible, for comparison and informed decision making. The rationale for OEHHA's use of human data for health-protective concentration (HPC) derivation is provided in the draft PHG document.

Comment 30: "Page 200: Section 6.2—the cancer potency derivation process is clearly described, though the significance of, for example, bolded text is sometimes confusing."

Response 30: OEHHA changed what text is bolded to improve clarity.

DR. HINDRIK BOUWMAN

Comment 1: "Overall, I found the use of literature excellent. Almost a 1000 papers and documents were directly considered, in addition to the references in the major reports that were used. The use of the literature in 2.1 (p18 and onwards) and in other sections, with tabulated summaries in Appendix 1 (p280 onwards), and with additional literature in Appendix 7 (p319 onwards) is evidence a very wide net cast. The librarians have done excellent work. Together with the additional literature in prior assessments, and actually identifying literature that were missed or not considered in the later, shows that a huge amount of work has been done. There were also instances of literature added that came out after the cutoff date, showing initiative and thoroughness.

Key documents and papers were rigorously selected and considered. It is very unlikely that any one or few papers would suffice for the aims of establishing Public Health Goals, but the combinations of papers selected, and the careful consideration of those that were not add tremendously to this work.

Positive, negative, ambivalent, and contradictory studies were considered and included in all category assessments. Contradictions particularly were well argued throughout and clear reasons for selection or rejection, for the current purpose, given.

I appreciate the bolding of relevant rows in the key tables and corresponding text."

Response 1: OEHHA acknowledges the comment.

Comment 2: "The consistency in style, grammar, and layout throughout was remarkable. This made it easy to read and anticipate what would be coming. I indicate a couple of instances for improvements, following in Specific Comments below. All too often, style, layout, and grammar of review documents vary due to multiple authors and various editorial input."

Response 2: OEHHA acknowledges the comment.

Comment 3: "I am not aware of any scientific issues not mentioned in this document that should have been considered."

Response 3: OEHHA acknowledges the comment.

Comment 4: "Suffice to say, that after reviewing the entire front text, I have found no problems with the approach, analyses, selection of methods, consideration of weak and strong papers and reports for the current purpose, impacts that these weak and strong points have had on conclusions, sample size, selection bias, participation rates, confounder identification and adjustments, consistent findings between human, animal, and mechanistic studies, the influence of co-variant pollutants, and reverse causality (amongst a host of others) were convincingly presented."

Response 4: OEHHA acknowledges the comment.

Comment 5: "Therefore, I have no hesitation in saying that the best has been done with the data and information available at the time that the Public Health Goals were derived for this Draft.

Undoubtable, there will be inputs and comments on the methods, assumptions and results of calculations, but when reading the argumentations and considerations of how each PHG was eventually calculated (especially for the noncancer issues, but equally for the cancer issues that I also examined), these are unlikely to have any major influence, if at all. This report assessment was not a 'hunt-for-the-lowest', but a 'search for-the-best'."

Response 5: OEHHA acknowledges the comment.

Comment 6: "From my background, I find it strange that both ppt and ng/L (or similar) were used inconsistently and interchangeably. Table S1 on p10 for instance, is probably the table that will be read most and quoted. There might be reasons for using ppt that I'm not aware of, but I suggest that wherever ppt is used, the equivalent mass-based concentration unit is provided to avoid ambiguity."

Response 6: The primary purpose of PHGs is to provide the basis for maximum contaminant level (MCL) development. Therefore, PHGs are often consulted and quoted in the regulatory context, where ppt units are used. In the PHG draft document, the footnote to Table S1 indicates that parts per trillion is equivalent to nanograms per liter or ng/L. Both ppt and ng/L units are used in Chapter 7, where final HPCs are calculated. Where equivalent mass-based concentrations are not provided, it was done for brevity/simplicity or, in the case of presenting environmental occurrence data, OEHHA used the units reported in the study publications.

Comment 7: "The Uncertainty Factors on P20 are good (+Appendix 2)."

Response 7: OEHHA acknowledges the comment.

Comment 8: "RSC on p20 and Appendix are 4 good."

Response 8: OEHHA acknowledges the comment.

Comment 9: "The argumentation on why dermal uptake as part of DWI (p21) was not considered should be better argued, and also brought in relation with Section 4.2. Specifically, the exclusion of dermal uptake via washing and swimming needs to be addressed. I understand the aim is purely related to PHG for drinking water, but clear reasoning and motivation should be given for excluding uptake from other purposes that may affect uptake from use of the same water."

Response 9: In response to this comment, Section 4.2 has been expanded regarding the issue of dermal and inhalation absorption and what this would mean for overall exposure.

Comment 10: "Chapter 3, no comments other than, excellent."

Response 10: OEHHA acknowledges the comment.

Comment 11: Referring to Chapter 4, "The last two complete sentences on P37 are not clear to me."

Response 11: In response to this comment, the penultimate sentence in the third paragraph of Section 4.3 has been expanded to define "growth dilution."

Comment 12: "Excellent discussion and comparisons of a good number of PBPK models."

Response 12: OEHHA acknowledges the comment.

Comment 13: "Section 4.7, very good comparisons between models."

Response 13: OEHHA acknowledges the comment.

Comment 14: Referring to Chapter 5, "5.1.4 Good argumentation and critical assessments."

"Consistent independent reinforcement from the various papers provides confidence of associations at appropriate levels of exposure."

Response 14: OEHHA acknowledges the comment.

Comment 15: "Chapter 6:

- Good consideration and weighing of the strengths of each study.
- Good selection of NOAEC/LOAEC values rather BMD methods in most cases.
- Confounding, selection bias, consistency, reverse causality, sample size, study design, relevant clinical outcomes, alternative explanations, and multiple studies were considered and compared.
- P182, the reasoning for the use of √10 to calculate UF for ADD was well done.
- The consideration of children in this regard was excellent and convincing.
- Section 6.2 (cancer text) I only scanned, as this was a bit out of my prevue. But, from what I read, seems to be the same quality as the prior text."

Response 15: OEHHA acknowledges the comment.

Comment 16: Referring to Chapter 6, "P183, make clear that the calculation was for PFOA. Suggest you add "The ADD for PFOA was calculated as:", as for PFOS on p197."

Response 16: In response to this comment, the suggested text has been added.

Comment 17: "Chapter 7: The way that relative source contributions were considered and worked in was exhaustive and convincing."

Response 17: OEHHA acknowledges the comment.

Comment 18: Referring to Chapter 7, "P225, state clearly that the first calculation is for PFOA, and the second for PFOS (here, mass-based units and ppt within the same formulas are striking, and I am not sure why ppt is used)."

Response 18: In response to this comment, it is now stated that the first and second set of calculations are for PFOA and PFOS, respectively (Sections 7.1.1 and 7.1.2 of the PHG document). Please see the response to Comment 6 from this reviewer as to why units are presented as ng/L and ppt.

Comment 19: "Table 8.1:

- I suggest adding the date each of these regulations or guidelines were published.
- I suggest adding the proposed (draft) PHG here as well, for comparison."

Response 19: In response to this comment, dates have been added and some values have been updated. The proposed PHGs have also been added to Table 8.1.

Comment 20: "*Overall assessment*

Based on the above, it is my opinion that the text provides a balanced and unbiased assessment with all due qualifications and respect given to all the authors and institutions, and that the PHG values have been derived with utmost care and consideration, and applicable for the intended purpose."

Response 20: OEHHA acknowledges the comment.

DR. VAIA LIDA CHATZI

Comment 1: "**Presentation of Results:** Please consider organizing each section by: 1) study design (cross-sectional, case-control, prospective cohorts), 2) exposure levels (occupational cohorts, high exposure population studies, general population studies), 3) area of research (e.g. number of studies performed in the US, Europe, Asia etc.), 4) consider describing exposure range in the studies included in the review, 6) consider describing quality assessment for studies included in the review, 7) consider performing a meta analysis, especially for the sections which include many studies with conflicting results."

Response 1: For suggestions 1-3, because there was such a large amount of complex and inter-related data, the large majority of the epidemiologic data reviewed in the draft PHG document is presented in tables. This allowed for a much more efficient, organized, and complete review. OEHHA considered re-sorting these tables using the criteria mentioned by the reviewer. However, it was concluded that the current sorting order best allows for the most effective and efficient review of the large amount of data presented. For example, the studies of immunotoxicity presented in Tables A7.3 and A7.4 of the PHG document include a large number of individual outcomes (e.g., antibody response, allergy, asthma, eczema, fever, cough, colds, and many others) that all fall within the broad classification of immunotoxicity. Because OEHHA found no reason to believe that every single aspect of the immune system, and thus every single individual immune-related outcome, is similarly affected by PFOS or PFOA, OEHHA sorted these tables by each individual outcome. Doing so allows the reader to see if there may or may not be consistencies within each outcome. This is important since the presence of consistent associations is a key element of causal inference (Hill, 1965). It would be very difficult for readers to evaluate this key criterion for any particular outcome if Tables A7.3 and A7.4 were sorted by study design or area of research rather than outcome.

Some of the other tables in the PHG document were sorted by age and sex. This was done because these appeared to be important subgroups for the particular outcomes being assessed (Tables A7.7, A7.8, A7.9, and A7.11). Again, sorting in this way allows the reader to more easily see if consistencies exist within these subgroups. If these studies were sorted by study design, exposure level, or location then important subgroup effects could be missed. It is possible that some readers will prefer the information in these tables to be sorted by some other factor. If so, information on a variety of factors is presented in the tables and readers can sort by whichever of these factors they wish.

For suggestion 4, information on the exposure levels in each study is already provided in the Appendix 7 tables. This includes the median or mean level, and some aspect of the exposure distribution, usually the interquartile range (IQR) or standard deviation (SD). OEHHA chose to present the IQRs and the SDs rather than the range (the single lowest and single highest values) because the range can be somewhat deceptive in the face of one or two outlying values. In contrast, the IQR and SD provide a better indicator

of the exposure levels experienced by most study participants. The important point here is to be able to distinguish studies that have generally higher or lower exposure levels, and the medians, means, IQRs, and SDs allow readers to do this.

For suggestion 6, please see the response to Comment 3 from Dr. Adgate. Information on the quality criteria used to evaluate each study was originally in Appendix 7. This has now been moved to the beginning of the main document (Section 2.2.2) to make it more evident and to highlight its importance.

For suggestion 7, most of the key elements of meta-analysis have already been done. This includes establishing initial hypotheses; formulating inclusion and exclusion criteria; performing thorough multi-faceted literature searches; abstracting data; displaying results; and quantitative and qualitative evaluations of bias, confounding, and causal inference.

The two components of a meta-analysis that have not been performed are calculations of summary effect estimates and heterogeneity statistics. With regard to summary effect measures, it is not clear that these would be helpful since the evidence linking PFOA or PFOS to cancer, lipid homeostasis, or liver toxicity is sufficiently strong without them. As discussed throughout the PHG document, the studies OEHHA used to develop health-protective concentrations and PHGs were high quality studies, that is, those with little evidence of important bias, confounding, or other errors. Perhaps it could be argued that calculating summary effect measures would help provide an “average effect” across many different studies, thereby diminishing the weight given to any one or two studies. However, this would entail combining data from the highest quality studies with those of lower quality studies, and therefore lead to a lower quality overall.

Another problem with calculating summary effect measures is that different studies used different exposure and outcome metrics. For example, some studies present results only as regression coefficients while others present results only as odds ratios. In order to calculate a summary effect measure, these different metrics would have to be converted into a single common metric. For some studies, this would not be possible, and these studies would have to be excluded (even if they were judged to be of high quality). For others, these calculations would be complex and require certain assumptions, and therefore add considerable uncertainty to the PHG process.

With regard to heterogeneity statistics, for many outcomes (e.g., thyroid hormones) the heterogeneity across different studies was so obvious that formal statistical tests were not needed. Another issue with heterogeneity statistics is that these tests frequently over- or underestimate the true degree of heterogeneity (Brockwell and Gordon, 2001; Huedo-Medina et al., 2006). In addition, the most commonly used statistical test for heterogeneity was designed for controlled clinical trials (DerSimonian and Laird, 1986). It was not designed for the types of observational epidemiologic studies that make up the human evidence on PFOS and PFOA.

In conclusion, OEHHA has considered performing meta-analyses. However, most of the key aspects of meta-analysis have already been performed. The remaining aspects, summary effect measures and heterogeneity statistics, are unlikely to add any significant advantages, but instead could add considerable complexity and uncertainty, and decrease quality overall.

Comment 2: "**Assessment of ecological studies:** Results from ecological studies should be interpreted consistently across different cancer types. For example, the study of Mastrontonio et al is presented as 'a study based on an ecologic design with very limited information on potential confounders', however, for testicular cancer, the same study is presented as 'an ecologic study, but there is no reason to suspect that ecologic fallacy or exposure misclassification caused this elevation, and no major confounders are obvious.'"

Response 2: In response to this comment, OEHHA modified the text, although the two statements cited by the reviewer are not mutually exclusive since the cause of most cases of testicular cancer are unknown (American Cancer Society, 2018). In order to avoid confusion, the mention of confounding in the second statement has been removed (Section 5.7.1 (under *PFOA, Testicular cancer*) of the draft PHG document).

Comment 3: "**Assessment of cross-sectional studies:** Appendix 7 (page 430) states that 'although the results of some cross-sectional studies are discussed in this review, OEHHA excluded cross-sectional studies of cancer from its main analyses given the long latency usually associated with environmentally caused cancer, and the possibility that cancer diagnosis or treatment could lead to medication use or a change in behaviors that could change PFOA or PFOS exposure levels.' Given that serum PFOA and PFOS measurements are generally thought to represent several years of exposure, the rationale for excluding cross-sectional studies should be described in more detail."

Response 3: The exact latency period of PFOA or PFOS caused human cancers is unknown. Although serum levels of PFOA or PFOS may represent a number of years of exposure, OEHHA could not find evidence that a single measurement may accurately reflect the very long latency periods seen for many other environmentally caused cancers. Furthermore, OEHHA could not find strong evidence that changes in serum PFOA or PFOS levels might not occur due to behavioral changes in people recently diagnosed with cancer, such as dietary modifications, treatments, or other lifestyle changes. Overall, these issues combined raise important concerns about the validity of any cross-sectional analyses of PFOA or PFOS and cancer.

Comment 4: "**Comparability of studies and dose-response:** Discussion of quantile cut-offs used across studies is inconsistent. Especially for type of cancers where studies show unusual dose-response relationships or have inconsistent findings, additional information about quantiles used and number of cases within each quantile should be included as this might offer a partial explanation."

Response 4: In response to this comment, information on quantile cut-off points has been added (Tables A7.21-A7.27).

Comment 5: "**Follow up:** For prospective studies, please describe the amount of time between exposure assessment and cancer diagnosis."

Response 5: In response to this comment, information on follow-up periods has been added to the summaries of studies as appropriate in Section 5.7.1 of the draft PHG document. Information on follow-up periods is already included in Tables A7.21-A7.27 of the draft PHG document.

Comment 6: "**Focus only on 2 chemicals (PFOA/PFOS):** Current chemical regulation depends on one-chemical-at-a-time risk assessment. It has been suggested that this approach provides inadequate protection against human exposure to PFAS because it fails to consider the mixture effects of exposure to multiple PFAS simultaneously. It would be useful to add a section on the perspective of other PFAS chemicals or PFAS mixtures in the discussion of main conclusions for cancer outcomes."

Response 6: The current PHG draft assessment is not meant to address health risks from human exposure to multiple PFAS, which is clearly a growing concern. This is a complex problem that goes beyond the scope of this document.

Comment 7: ***"*Quality Assessment:** Please provide some additional information on how this was completed, including what the possible ratings were (i.e., 'low,' 'probably low'), domains/characteristics evaluated, and an example of how they were determined (e.g., 'For a study to be rated 'low' risk of bias from confounding, the analysis must have evaluated the following confounders:….)."

Response 7: Please see the response to Comment 3 from Dr. Adgate regarding study quality.

Comment 8: "In addition, there is no discussion on the quality of evidence overall, publication bias, or mention of any studies that were excluded."

Response 8: With regard to study quality, please see the response to Comment 3 from Dr. Adgate.

With regard to publication bias, OEHHA had considered this bias but the focus of the draft PHG document was on those biases most likely to have important effects. Publication bias is thought to primarily affect smaller studies (Egger et al., 1997), and the basis of most statistical tests for publication bias involve the theory that true effects are centered around the results of higher quality, larger studies (Sterne et al., 2000). Importantly, OEHHA chose very large high quality epidemiologic studies as the basis of its PHG, studies that are unlikely to be affected by publication bias. For example, the Vieira et al. (2013) study, one of two studies used to calculate the cancer health-protective concentration for PFOA, was of very high quality (Section 6.2.1 of the draft PHG document) and involved over 7,000 people. Given the availability of large high

quality studies like this one, and given the widespread interest in PFAS among the research community (e.g., a PubMed search of PFOA will return over 4,000 studies), OEHHA has concluded that publication bias is unlikely to have had an important impact on developing the PHG.

Exclusion criteria are already presented in Appendix 7, and excluded studies and the reasons for their exclusion are already provided in Table A7.28 of the PHG document.

Comment 9: "**Sex specific effects:** Did any studies provide different estimates by sex? If so, please describe."

Response 9: Important subgroup effects, including those based on sex, are provided in Tables A7.3-A7.27 of the draft PHG document (under the sections labeled "Results," "Notes," or "Subgroup only"). Overall, important, consistent, and convincing differences by sex were not seen for the outcomes used to develop the PHGs.

Comment 10: "**Differential effects by ethnicity/race:** Did any studies provide different estimates by race/ethnicity? If so, please describe."

Response 10: Too few studies provided information by race or ethnicity to make firm conclusions regarding these factors. As mentioned in Sections 6.1.1 and 6.1.2 (under *Acceptable Daily Dose Calculation*) of the draft PHG document, the lack of information on race and ethnicity was a part of the reason why an uncertainty factor was applied to the acceptable daily dose calculations.

Comment 11: "Please comment on whether studies were specifically designed to look at a specific cancer type, or if many/all cancers were considered. Studies that looked at many cancers and did not control for multiple comparisons may have significant findings that occurred by chance. This could be noted in the Appendix tables or in the text."

Response 11: In response to this comment, it is now stated at the beginning of Section 5.7 of the draft PHG document that comparisons issues were considered when interpreting findings. It should be noted that controlling for multiple comparisons has several major disadvantages (Rothman, 1990). A better way to avoid the problems associated with multiple comparisons is to place greater emphasis on those findings that are seen across multiple study populations. This is what OEHHA has done, and all of the study findings used to develop health-protective concentrations are supported by findings from other studies. This is discussed throughout the draft PHG document.

Comment 12: "**Appendix Tables:**

- Please describe median/mean exposure levels and range of exposure levels for each one of the studies included in the table.
- Please indicate whether the study examined only the specific type of cancer or many other cancer types.
- Some tables list "weaknesses" instead of "potential weaknesses" in the notes column. Does this distinction mean anything?"

Response 12: Mean or median levels are already provided in the tables. As noted above in Comment 1 (suggestion 4) ranges can be deceptive in studies with outlying values. In addition to the exposure means or medians and IQRs or SDs, exposure category cut-off points are also now provided (please see the response to Comment 4). As a whole, the combination of all of these values should provide readers with a good picture of the exposure distribution in each study.

Because the tables for the different cancer types are all adjacent to each other, and because the study designs are given, the tables indicate which studies involved multiple cancer types. In addition, if readers are interested in this issue they can refer to the publications themselves, which are fully referenced in the tables and bibliography. Finally, please see the response to Comment 11 regarding the multiple comparisons issue.

In response to Comment 30 from this reviewer, the "Potential weaknesses" and "Weaknesses" headings have been removed from tables in Appendix 7.

Comment 13: "**Appendix-New Figures:** I would strongly advise to create coefficient plot figures for the studies that have the most conflicting results or even better to conduct a meta-analysis and include the results of the meta-analysis in the appendix."

Response 13: Please see the response to Comment 1 regarding meta-analysis. With regard to coefficient plot figures, in most instances, the presence or absence of heterogeneity was so obvious that coefficient plot figures were not needed. Even where heterogeneity was not obvious, coefficient plot figures would not be helpful. This is because for almost every outcome assessed, studies presented results using a very wide variety of different outcome metrics (e.g., odds ratios, mean differences, regression coefficients, $\log_2$ PFOA, $\log_{10}$ PFOA, lognormal PFOA, 1 ng/ml increase in PFOA, PFOA quantiles, etc.). Because of this, it would be very difficult, if not impossible, to produce a single coefficient plot figure that would include all or even most of the studies. A number of different plots could be produced, one for each different type of exposure and outcome metric combination. However, the primary purpose of a coefficient plot figure is to provide a simple, condensed, and easy-to-read visual display of all findings in one place. This would be negated by having many different plots for each individual health outcome.

Comment 14: "Bladder cancer:

- Please present summary of results by type of studies and exposure groups (occupational vs general population).
- A new study Li et al 2022 shows modestly elevated hazard ratio for bladder cancer (HR 1.32; 95%CI 1.01–1.72).
- Please describe the discrepancy in results between the two studies published in the general population (Eriksen et al 2009 and Li et al 2022)."

Response 14: Information on the type of study, study design features, and exposure levels are already provided (Table A7.21). In response to this comment, additional text has been added to the beginning of Section 5.7 to indicate that this information can be found in the study summary tables in Appendix 7 (Tables A7.21-27).

Regarding the Li et al. (2022) study, participants were exposed to very high levels of multiple PFAS, and the effects of the individual PFAS cannot be distinguished. In response to this comment, a discussion of this study has been added to Section 5.7.1 (under *PFOS, Other studies*) of the draft PHG document and the inability to distinguish the effects of the different PFAS is also noted.

Regarding the discrepancy in results between Eriksen et al. (2009) and Li et al. (2022), it is hard to argue that Li et al. (2022) is a "general population" study since it involved an exposure scenario that has likely never been encountered by any other large population group worldwide. And as noted above, participants were exposed to high levels of multiple PFAS. As such, it is unclear which PFAS or combination of PFAS were responsible for the elevated risks. This is in contrast to Eriksen et al. (2009), which involved much lower ("general population") exposures and provided results specifically for serum PFOA. Overall, because of these major differences, a direct comparison of these studies would not be helpful. Regardless, readers wishing to do this can easily do so since descriptions of both studies are included in the draft PHG document (Table A7.21) and full references to both publications are provided.

Comment 15: "**Breast cancer:**

- Please describe study area and PFAS levels. For example, the study by Bonefeeerl-Jorgensen et al was conducted in the Inuit population in Greenland. Another study that was conducted in the same population (Wielsoe et al., 2017) is not reported in the review summary.
  Wielsoe M, Kern P, Bonefeld-Jorgensen EC. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. Environ Health. 2017;16(1):56.
- Please describe differences in exposure levels between studies. The two studies conducted in an area near a chemical plant (DuPont, West Virginia), although reported in Table A7.22, are not discussed in the summary of human evidence for breast cancer (page 140):
  Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 2013;121(11-12):1313-8.
  Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environ Health Perspect. 2013;121(3):318-23.:
- Report on studies conducted in Asia. One hospital-based case-control study from Taiwan which showed null results between PFOA exposure and breast cancer is missing from the summary of human evidence for breast cancer. The authors

claim that they did not include it due to its cross-sectional design, but the design is case-control and other studies without prediagnostic samples for PFAS measurements were included in the review.
Tsai MS, Chang SH, Kuo WH, Kuo CH, Li SY, Wang MY, et al. A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. Environ Int. 2020;142:105850.

- Discussion of the use of pre-diagnostic vs samples collected after diagnosis: Please describe how many studies utilized pre-diagnostic samples.
- Please compare year of sample collection between studies and how this may affect the reported results.
- Are there any studies conducted in African American or Hispanic populations? If yes, please describe effect estimates for these populations."

Response 15:

- The Bonefeld-Jorgensen et al. (2014) study cited in the summary involved women from the Danish National Birth Cohort. They were not from an Inuit population in Greenland. This was noted in Table A7.22 but is also now noted in the breast cancer summary for PFOA in Section 5.7.1 of the draft PHG document. The Wielsoe et al. (2017) study involved an Inuit population but was excluded because it used a cross-sectional assessment of exposure. This was noted in Table A7.28. Study areas and PFAS levels are already described throughout the summaries and tables.
- As for differences in exposure levels between the Barry et al. (2013) and Vieira et al. (2013) studies, both studies took place in the C8 study area in the Mid-Ohio Valley, so exposure levels are similar. These studies are now mentioned in Section 5.7.1 (under *PFOA, Breast cancer*) of the PHG document. With that said, it should be noted that the summaries were not meant to be detailed and exhaustive lists or descriptions of each study. The latter is the purpose of the associated tables, and details of the Barry et al. (2013) and Vieira et al. (2013) studies were already included there.
- Regarding studies conducted in Asia, the design of a study involves many different components, such as subject selection, exposure assessment, outcome assessment, statistical analyses, and many others. While it is true that Tsai et al. (2020) selected participants using a case-control design, the exposure assessment was cross-sectional (Tsai et al., 2020). The latter was by far the more critical aspect of the design since it was the major source of uncertainty and potential bias. As noted in Appendix 7 (under *Cancer, Literature search and methods*) of the draft PHG document, cancer studies using a cross-sectional assessment of exposure like Tsai et al. (2020) were excluded because of concerns regarding latency and reverse causation. For certain health outcomes other than cancer, these concerns were less important, and cross-sectional designs were considered a valid method for evaluating true effects.
- Regarding studies that utilized pre-diagnostic samples, it is already mentioned that cross-sectional studies of cancer (those that assessed PFAS near, at, or after the

time of cancer diagnosis) were excluded (Appendix 7 of the draft PHG document under *Cancer, Literature search and methods*). However, in response to the reviewer's comment, this is now also mentioned at the beginning of the cancer summaries (Section 5.7). Some studies used PFOA serum levels in samples collected many years before cancer diagnosis, and this information is already included in Tables A7.21-A7.27 of the draft PHG document.

- Regarding the comparison of sample collection year between studies, information on sample year is now provided in Tables A7.21-A7.27. As expected, OEHHA found no clear association between sample year and study results.
- Regarding studies conducted in African American or Hispanic populations, there were no cancer studies that specifically focused on these groups. As already mentioned above and in the document, the lack of information in different race or ethnic groups is a source of some uncertainty.

Comment 16: Regarding kidney cancer, "This section should go into more detail, even though is discussed in Chapter 6. The authors could provide here a brief overview of the most significant findings and discussion of any conflicting results."

Response 16: In response to this comment, a brief summary of several significant findings is now presented in Section 5.7.1 of the draft PHG document, under *PFOA, Kidney cancer*.

Comment 17: Regarding liver cancer, "The summary paragraph should discuss all studies reported in Table A7.24, and not only the results of the high exposure occupational studies."

Response 17: Please see the response to Comment 15 from this reviewer. These summaries are not a complete replication of the information already provided in the tables. As it stands, OEHHA's risk assessments for PFOS and PFOA are thorough and comprehensive, and simply repeating information would not improve the overall quality of this work.

Comment 18: Regarding prostate cancer, "Two studies are discussed in this section, but there are several others listed in Table A7.26. Do these two best represent the all the available research on this subject? Are they in agreement with the conclusions of the other studies in Table A7.26? Additional justification should be given for why cancer screening might be a confounder. Is screening related to PFOA exposure? Were some people more likely to be screened than others? If cancer screening is likely to confound the PFOA-prostate cancer relationship, we might have this concern for other cancers as well (especially breast cancer)."

Response 18: In response to this comment, the other prostate cancer studies are now mentioned in this section. As noted above, they were not initially mentioned because this summary was not a full list of all studies and all study details. The reason why OEHHA gave particular focus to the two studies mentioned by the reviewer is that they

reported widely discrepant results, yet were based on the same occupational cohort. Given the high PFOA-related risks reported in the first study, an evaluation of the possible reasons why the second study reported much different results was a particularly important topic.

The point about cancer screening was made in an effort to be complete and to cover a potential bias that is frequently a concern in studies of prostate cancer. However, since cancer screening is unlikely to be related to PFOA, this issue is relatively unimportant and based on the reviewer's comment, has now been removed.

Comment 19: Regarding testicular cancer, "Although the 3 studies are consistent in finding increases of testicular cancer among the highest PFOA exposed groups, two of these studies rely on overlapping populations based on the C8 Science Panel study (Barry et al., 2013; Vieira et al., 2013). No cancer studies of general populations have been published on PFOA and testicular cancer. Additionally, the ecological study results (Mastrantonio et al., 2018) could not be used to investigate dose-response relationship and due to lack of quantitative exposure assessment, it is not possible to convert exposure from this study in a common exposure scale."

Response 19: OEHHA agrees, and all of this information is already conveyed in the summary or associated table (Table A7.27).

Comment 20: Regarding PFOS and liver cancer, "Rather than stating that there was "no clear association," please describe what they study did or did not find – was the relationship not statistically significant? Was the effect very small, or was there no dose-response relationship?"

Response 20: This information has been added to Section 5.7.1 of the draft PHG document under *PFOS, Liver cancer*.

Comment 21: Regarding PFOS and other cancer types, "Please describe (or list) which types were examined."

Response 21: This information is available from the publications, which are fully referenced in this section. OEHHA did not provide extensive details on certain cancer types because this information is already available in the underlying publications and because they were not useful for developing the PHGs.

Comment 22: Regarding Chapter 6 (*Dose-Response Assessment*), "Overall, this chapter is well-written and describes in detail the two selected studies (Vieira et al. 2013 and Shearer et al. 2021) for dose-response assessment and cancer slope factor (CSF) calculations."

Response 22: OEHHA acknowledges the comment.

Comment 23: "**Page 204, Selection bias:** Shearer et al. 2021 being a convenience sample should not, on its own, introduce selection bias. Characteristics of participants

selected for a prospective cohort would not compromise the internal validity of the study, though the results may or may not be generalizable to a general population with different characteristics."

Response 23: OEHHA agrees that the effect of selection bias on internal validity is likely to be minimal. A discussion of generalizability to the US population is already provided in Section 6.2.1 of the draft PHG document under *Generalizability*.

Comment 24: "**Page 209, Exposure misclassification:** Residential addresses were only available at the time of diagnosis for the Vieira et al. study, so there is the assumption that participants had been living at the same address for several years prior to diagnosis. Please describe how this can or cannot affect misclassification of exposures. Most likely this results in non-differential exposure misclassification, but this needs to be in the report."

Response 24: The conclusion that this bias is most likely non-differential is already provided in Section 6.2.1 of the draft PHG document under *Exposure misclassification*. The fact that residences were only available at the time of diagnosis is also already in the draft PHG document (Table A7.23), although this has now been added to the section on exposure misclassification in Section 6.2.1 as well.

Comment 25: "**Exposure levels:** Shearer et al and Vieira et al do not find effects at the same exposure levels. For example, the 'medium' exposure level in Vieira included PFOA levels between 12.9 and 30.7, similar to the fourth quartile in Shearer (7.3-27.2), but the magnitudes of association (OR=1.2 in Vieira and OR = 2.6 in Shearer) and statistical significance (non-significant in Vieira and significant in Shearer) are different. Any implications for the PFOA-RCC relationship and/or discussion of differences in study design that would account for this should be included."

Response 25: In response to this comment, a paragraph discussing these differences has been added to Section 6.2.1 of the PHG document, under *Results*.

Comment 26: Regarding the organization of Chapter 5, "Please consider organizing each section in this chapter by 1) study design (cross-sectional, case-control, prospective cohorts), 2) exposure levels (occupational cohorts, high exposure population studies, general population studies), 3) area of research (e.g. number of studies performed in the US, Europe, Asia etc.), and/or 4) Age of study participants (adult studies vs studies conducted in children). Please also describe exposure range in the studies included in the review (e.g. median exposure levels for PFOA and PFOS per type of study)."

Response 26: Please see the response to Comment 1 from this reviewer regarding the resorting of these studies.

Comment 27: Regarding Chapter 5, "Consider performing a meta-analysis, especially for the sections which include many studies with conflicting results. Coefficient plots

may also help with these cases if a meta-analysis is not possible. Systematic reviews with meta-analyses have already been published for some outcomes and citing these findings may also support the OEHHA's conclusions."

Response 27: Please see the responses to comments from this reviewer regarding meta-analysis (Comment 1) and coefficient plots (Comment 13).

A number of meta-analyses and systematic reviews are already cited (Ballesteros et al., 2017; EFSA, 2020; Luo et al., 2020; Steenland et al., 2018; US EPA, 2016a, 2016b; Kennedy et al., 2004; ATSDR, 2021). In response to this comment, the meta-analyses of Bartell and Vieira (2021) and Costello et al. (2022) are also now cited in Sections 5.7.1 and 6.1.1, respectively.

Comment 28: Regarding studies identified after the initial literature review (Table A7.29), "Some of these studies are presented in subsections (for example the study of Abraham et al, 2020 for immunotoxicity) but not all of them. This should be consistent throughout the review."

Response 28: Abraham et al. (2020) was a particularly important study because it was of generally high quality, it involved a key outcome (vaccine response), and it included dose-response data that could be used to calculate a point of departure (Abraham et al., 2020). These issues are already discussed in Sections 5.1.1 and 6.1.1 of the draft PHG document). None of the other studies in Table A7.29 of the draft PHG document met all of these same criteria, and therefore were not discussed in detail in the main document.

Comment 29: Regarding quality assessment in Chapter 5, "Please provide more information about quality ratings (e.g., how a study earns a 'high quality rating', or if any studies were excluded due to quality). The format of Table A7.12. is a good representation and can be used for all health outcomes in Chapter 5."

Response 29: Please see the responses to Comment 3 from Dr. Adgate and Comment 8 from this reviewer regarding study quality and exclusion criteria, respectively.

Table A7.12 (now Table A7.11) of the draft PHG document was created to provide a more in depth review of the studies on serum lipid levels. This was needed for several reasons. First, the currently available data on PFAS and serum lipid levels was exceptionally large, with over 80 studies providing over 2,000 different results. Second, this database was complex. Most studies provided results for four or more different types of lipids, four or more different PFAS, several different subgroups, and several different types of statistical analyses. Third, somewhat complex inter-relationships exist between the different types of lipids. For example, LDL and high-density lipoprotein (HDL) are both a part of TC but each has an opposite effect on cardiovascular disease risk. Another example is the well-known differences in lipid levels and associated disease risks across different subgroups, which must be considered including factors like age, sex, and pregnancy status. A fourth reason for this more in depth analysis is that a significant percentage of all of the studies on this outcome came from a single

underlying source, NHANES. Part of the reason this table was created was to see if results differed depending on whether or not they came from this underlying source.

In conclusion, Table A.7.11 was created as an additional tool to help sort through the large and complex database that currently exists for PFAS and serum lipid levels, issues that were not necessarily present for all of the other outcomes OEHHA had assessed.

Comment 30: "**Appendix 7:** Please consider organizing the Appendix 7 tables in a harmonized format for all health outcomes, so that all tables present information in the same way (eg: Authors and year, Location, Type of Study, Study population, Age of Study participants, No of subjects, Exposure assessment, Disease Outcome/Outcome assessment, Covariates, Results, Notes). In particular, for sections with many papers that each look at several outcomes (e.g., immunotoxicity), it is difficult to reference the tables when they are organized by outcome, and there are multiple rows per study. It may help to create separate tables for each outcome in this case. It may also help to group the studies by design (cross-sectional, case-control, cohort, etc.) where possible. Also, please be consistent in adding "potential weaknesses" to the notes section. If these notes are present for some studies and missing for others, it implies that those studies had no weaknesses."

Response 30: Almost all of the tables in Appendix 7 of the PHG document are already organized in a harmonized format and already include the sections mentioned by the reviewer. The exceptions are Tables A7.10, A7.11 and A7.12, which are organized differently for the general reasons given in the preceding response.

Tables were organized by outcome for the reason given in response to Comment 1 (suggestions 1-3) from this reviewer. OEHHA considered separate tables but judged that this would not be a marked improvement. The document is already over 600 pages and is already the most thorough and comprehensive risk assessment of PFOA and PFOS published to date. Having separate tables for each individual outcome, for which there are many, would make the document markedly longer and more difficult to read. Because the current tables are already sorted by outcome, and because these outcomes are clearly identified, finding all of the studies on any particular outcome should be very easy without the need for separate tables.

The "Potential weaknesses" section was meant to provide information on some major, common, or otherwise noteworthy weaknesses that were not already covered in other parts of the table. OEHHA agrees with the reviewer that leaving this section blank may give a few readers the false impression that the study has no weaknesses. For this reason, the "Potential weaknesses" heading has now been removed. In addition, information has now been added about the purpose of the Notes column (Appendix 7 of the draft PHG document, under *General Methods*).

Comment 31: Regarding human evidence for immunotoxicity, "*Antibody response*: When discussing results, be clear which studies are prospective vs. cross-sectional, and describe studies by age group (eg <=1 years of age, 1-5 years, >5 years)."

Response 31: This information is already presented in Tables A7.3 and A7.4, which are cited at the beginning of Section 5.1.1 of the draft PHG document. Restating the information from these tables in Section 5.1.1 would be repetitive and not improve the document.

Comment 32: "Please consider adding/describing the study by Timmermann et al. (2020), which examined the association of PFAS exposure and antibody response to measles vaccination among children from Guinea-Bissau."

Response 32: Timmermann et al. (2020) is already cited in Table A7.29 of the draft PHG document. As noted in this table, its findings support a causal association between PFOA and PFOS and decreases in antibody response, consistent with OEHHA's current conclusions.

Comment 33: "Please also consider adding or describing Abraham et al. (2020), which showed a consistent inverse association between levels of vaccine antibodies for tetanus and diphtheria (IgG) in relation to PFOA blood serum concentrations among 1-year-old children."

Response 33: As already noted at the end of Section 5.1.1 of the draft PHG document, this study is not included in some of the tables because it was identified after OEHHA's primary literature search. Regardless, this was an important study for the reasons given above in response to Comment 28, and as such is the topic of considerable discussion in throughout document.

Comment 34: "In Table 5.1.1, values of the outcome and exposure should be included. Please also consider including confidence intervals, and the difference between the 5 years pre and 5 years post needs to be further explained (are these the same children, before and after vaccination? Or different groups? It is not clear from the table notes). A meta-analysis might also help understand findings for overlapping study conditions. In table 5.1.3, please indicate in some way which studies are prospective."

Response 34: Information on the outcome and exposure values are already provided in the heading of this table (i.e., the values are the percent change in vaccine response for each 2-fold ng/ml increase in serum PFOA or PFOS). Information on the probability that each finding in Table 5.1.1 is due to chance (which is the primary purpose of confidence intervals) is also already provided (please see the table footnotes about statistically significant results). Finally, exposure levels and confidence intervals or p-values are also already provided for these studies in Tables A7.3 and A7.4 of the draft PHG document.

With regard to the pre- and post-vaccination results, it appears that these results mostly involve the same children although this is not clearly explained in the underlying publication (Grandjean et al., 2012). This is now noted in the footnotes of this table.

A key assumption of most meta-analyses is that the included studies are independent. Since the large majority of the results in Table 5.1.1 come from only two different cohorts, a meta-analysis of the results in this table would violate this key assumption.

In response to this comment, prospective studies are now identified in Table 5.1.3.

Comment 35: "*Infectious disease*: Please specify how many new studies have been published since NTP 2016, their characteristics, and whether anything new information is added. For lower respiratory tract infections, please discuss the magnitudes of these associations.

Additionally, if 3 out of 4 studies found statistically significant results, these findings should be discussed further unless there is some reason not to (such as extremely small effect sizes, study quality issues, or conflicting directions of association). In general, the statistical significance will mean little if the magnitude of the association is not described.

This section should take into account study quality and design, with more focus on high quality/well designed studies, while low quality studies may be summarized briefly. Please also discuss the methodology in how health outcomes (infectious diseases) were measured, as this may affect the quality of the studies, and what efforts were made to control for known confounders and effect modifiers that may contribute to infectious disease susceptibility (e.g. family history, BMI, nutrition, stress).

Consider adding the study by Dalsager et al. (2021) which showed that prenatal PFAS levels were associated with increased hospitalization rates and higher risk of lower respiratory tract infections in childhood."

Response 35: The number of new studies identified, study characteristics and magnitudes of association are provided in Appendix 7, although new wording on this has now been added to improve clarity (Section 5.1.1 of the draft PHG document).

The magnitudes of the associations reported in these three studies are already provided in the PHG document (Table A7.3). Although the directions of the associations were not conflicting, the presence or absence of associations were. That is, associations were seen in three of the four studies but were not seen in the large prospective study by Manzano-Salgado et al. (2019). This is already noted in the draft PHG document. In addition, none of the three studies identifying an association provided information that could be used to estimate dose-response relationships or calculate health-protective concentrations. This is now noted in Section 5.1.1 (under *Infectious diseases*) of the draft PHG document.

Study design features, methods for outcome assessment, factors used to judge study quality, subgroup information, and efforts to control for potential confounders are all already presented in Tables A7.3 and A7.4 of the PHG document.

Dalsager et al. (2021) and its impact on developing the PHG is already presented in the PHG document (Table A7.29).

Comment 36: "*Hypersensitivity*: In addition to the organization suggestions described in the general comments, consider distinguishing between exposure assessment methods (maternal blood samples vs. cord blood samples).

Please be specific on the magnitudes of association.

For asthma, even if all studies are all cross-sectional, an attempt should be made to describe effects and consistency of the effect estimates across studies. Additionally, the text implies that all or most studies are cross-sectional but goes on to describe several prospective studies (PFOA concentrations at 5 years with asthma up to age 13, PFOA in maternal/cord blood and asthma in childhood). This should be clarified.

It may also be useful to describe the potential effects of PFAS on asthma by various age groups and sex (if information is available) since sex disparities and changes by age are frequently reported in asthma research.

For eczema, how many studies were available, and how many of those were not clear or inconsistent? What were their designs, quality?"

Response 36: Information on exposure assessment methods and magnitudes of the associations is provided in Tables A7.3 and A7.4 of the draft PHG document.

An overall conclusion regarding the effects and consistency of the studies of PFOA and asthma has now been added to Section 5.1.1 of the draft PHG document, under *Hypersensitivity*.

The document does not say that all recent asthma studies are cross-sectional, only that three of them are. Regardless, in order to improve clarity it is now noted that several prospective studies have also been published.

Information on ages and sex (when available) is already provided in Table A7.3 of the draft PHG document. It is now noted in Section 5.1.1 (under *Hypersensitivity)* that clear differences were not seen by age and sex.

For eczema, nine studies were available and this is now stated in Section 5.1.1 of the draft PHG document, under *Hypersensitivity*. As already stated, most of these did not find clear or consistent associations. These results are summarized in Table A7.3 of the draft PHG document. Information on study design and study quality is also provided in this table.

Comment 37: "*Other outcomes*: A table would be helpful to summarize these findings (number of studies, direction of effect & magnitude, quality/confidence assessment)."

Response 37: All but two of the studies discussed in the "Other outcomes" section were previously reviewed by the National Toxicology Program (NTP, 2016). The NTP (2016) document is referenced here and in numerous places throughout the draft PHG document. OEHHA has concluded that the NTP (2016) analyses are generally of high quality, and except for describing a few critical studies, OEHHA judged that a detailed replication of the NTP document was not needed here. Details of the two studies mentioned in this section, as well as those of several other studies published after the NTP (2016) review, are already described in Tables A7.3 or A7.4 of the PHG document.

Comment 38: Regarding Section 5.1.4 (*Conclusions*), "When discussing results from studies identified since the NTP (2016) review, it's helpful to include in the text the number of studies that actually is (ie, page 69: 'For other outcomes such as colds or gastroenteritis, studies published since the NTP review did not identify clear associations' – how many studies is this?). This would allow readers to understand how consistent the literature is, especially in recent publications. The discussion of potential for bias/sources of possible bias should also expand to outcomes other than decreased antibodies responses (e.g., asthma, infections etc.), at least briefly."

Response 38: In response to this comment, information on the numbers of studies has been added to Section 5.1.1 of the PHG document. OEHHA focused its discussion of bias here on studies of vaccine response because this was the immune outcome with the most consistent findings and most appropriate data for estimating dose-response. As such, it is one of the outcomes selected for point of departure (POD) calculations. The potential biases in the studies of asthma, infections, and most other immune related outcomes were similar to those discussed for vaccine response, and the wording throughout in this section has now been changed to reflect this.

Comment 39: "What makes the studies in Table A7.1 'more informative'? Page 322: 'A brief review of the results of a few of the more informative studies is shown in Table A7.1.'"

Response 39: In general, larger, more generalizable studies that assessed prevalent factors, and presented clear results and methods were selected. This is now stated in Section 2.2.2 of the draft PHG document (in response to Comment 25 from Dr. Adgate, criteria used by OEHHA to determine the quality of human studies were moved from Appendix 7 to Section 2.2.2).

Comment 40: Regarding human evidence for liver toxicity, "There should be more discussion of the findings in children, given the diversity of study populations (the Khalil study was in a very small group of obese children, Attanasio was teens and general population, Mora was younger birth cohort). These differences might have implications for the interpretation of inconsistent results."

Response 40: The fact that the ages of the children in these three studies differed, and that their findings also differed is already mentioned in Section 5.2.1. In response to this comment, additional information about these studies have been added to this section, none of which change the conclusion that findings in children overall are less consistent than those in adults.

Comment 41: Regarding Section 5.2.4 (*Conclusions*), "There should be additional discussion about differences in results between children and adults. Most studies in children do not show clear relationships between PFAS and liver enzymes, while many adult studies do. The study in children with NAFLD (Jin et al., 2020) shows that the severity of liver disease may be associated with PFAS exposure and may add to the discussion."

Response 41: Please see the response to the preceding comment: further information has been added about the studies in children. The reviewer's comment includes the most important point here: findings in children are much less consistent than those in adults, and this is already acknowledged in Section 5.2.1 of the draft PHG document. It is also noted that the reason for this is currently unknown. Further discussion of the possible reasons for these differences would be mostly conjecture and well beyond the scope of this document.

With regard to Jin et al. (2020), this study is already included in the PHG document (Table A7.28). Since it only involved children with non-alcoholic fatty liver disease (a very rare condition), and its findings have yet to be replicated, its results had essentially no impact on developing health-protective concentrations.

Comment 42: "Regarding the small effect sizes for PFOA and liver enzymes: most studies transformed the exposure and/or outcome, which makes it difficult to understand the actual magnitude of the association. Please describe further how much of an increase (in liver enzyme levels, or only ALT) would be significant for health. The main conclusion is that a doubling of PFOA results in a 6.8% increase in ALT, but the text should give an example of 1) how much of an increase that would be for an average person, in units of ALT; and 2) how much PFOA represents a 'doubling' for an average person. This would emphasize the significance of the exposure, especially given the differences in study designs (occupational vs. population based)."

Response 42: As already discussed in detail in Section 6.1.1 of the draft PHG document under *Clinically relevant outcome*, a major advantage of using the Gallo et al. (2012) study to calculate the acceptable daily dose for PFOA is that the results are presented as odds ratios for having an ***elevated ALT***. And, the cut-off point the authors used to define an elevated ALT is based on a very widely used, well supported clinical criterion, one that has been clearly and consistently linked to high levels of disease and mortality in human populations. The relevance, importance, and value of these cut-off points for risk assessment are already discussed in that section. The "main conclusion" is not that a doubling of PFOA causes a 6.8% increase in ALT. Rather, the main conclusion here is that PFOA increases the odds of having clinically important levels of

ALT. Given this, a complicated and extensive discussion about the exact clinical (or societal) implications of a 6.8% increase in ALT is not needed and would mostly be a distraction.

Comment 43: "There is also consistent evidence for a relationship between PFOS and ALT, even though the studies are primarily cross-sectional and there is no huge prospective study like (Darrow et al., 2016). The animal evidence also supports this relationship. This should be emphasized more, even if it does not allow an absolute determination of causality."

Response 43: OEHHA agrees and it is now mentioned in Section 6.1.1 of the draft PHG document that some studies have linked PFOS to ALT.

Comment 44: "The liver toxicity search [Appendix 7] did not include liver disease terms like NAFLD, steatosis, inflammation, etc. This should be justified, if there was a reason for it. Rantakokko et al. (2015) is listed in the table of excluded studies, because it was conducted in bariatric surgery patients (Table A7.28). There should be additional justification for excluding this population. Obesity, including severe obesity and related complications, is common worldwide, and any reason why the relationship between PFOA/PFOS exposure and liver disease would be substantially different in this population should be described."

Response 44: It was judged that the key words already included in the search string such as "liver" or "hepatic*" would also identify publications with the words mentioned by the reviewer. However, in response to the reviewer's comment OEHHA performed a follow-up PubMed search that included these other words or phrases. As expected, no new relevant articles were found.

While it is true that obesity is very common, having bariatric surgery is not (Angrisani et al., 2017). Rantakokko et al. (2015) was excluded because the impact of having this surgery, or preparing for it (either by the surgical team or by the patient themselves), on serum PFAS concentrations is unknown (Rantakokko et al., 2015). This is now stated in Table A7.28 of the PHG document.

Comment 45: "In Table A7.5 and A7.6, the type of log transformation (or lack thereof) should be described for continuous exposures and outcomes. This is done inconsistently in the Tables, and these studies made many different choices."

Response 45: In response to this comment, this information has now been added to Tables A7.5 and A7.6 of the draft PHG document.

Comment 46: "There is another study by Jain (2018) that was not listed in the liver tables and was not in the table of excluded studies [in Appendix 7]. It overlaps with other NHANES populations (including Jain & Ducatman 2018a) but the analysis is different and may be relevant.

- Jain RB. Concentration of selected liver enzymes across the stages of glomerular function: the associations with PFOA and PFOS. Heliyon. 2019 Jul 29;5(7):e02168. doi: 10.1016/j.heliyon.2019.e02168. PMID: 31388590; PMCID: PMC6667701."

Response 46: This publication (Jain, 2019) overlapped with Jain and Ducatman 2018b and is already cited under the "Notes" column of the latter in Tables A7.5 and A7.6 of the draft PHG document. It was not listed in the bibliography by mistake but this has now been corrected.

Comment 47: Regarding human studies of lipid homeostasis, "Study quality is given a lot of attention in Tables A7.11 and A7.12. Please consider describing the summary of these findings in this section [Section 5.3.1]. More discussion should be provided for the PFOS findings. Specify the number of studies that examined PFOA vs. PFOS, and the number of studies that were cross sectional vs. longitudinal. Please see my previous comment regarding section organization and modify accordingly."

Response 47: Summaries of the study quality information presented in Tables A7.11 and A7.12 (now Tables A7.10 and A7.11 of the draft PHG document) were already presented in Section 5.3.4 (*Conclusions*). However, in response to the reviewer's comment, these have now been expanded and have been moved up into Section 5.3.1. The numbers of studies assessing PFOA and PFOS, and the numbers of studies that were cross-sectional vs. longitudinal are now provided.

Comment 48: Regarding Section 5.3.4 (*Conclusions*), "This section is very well organized and provides a very thorough bias discussion. Consider using this outline in all other conclusions' sections of this chapter."

Response 48: Studies of different outcomes varied greatly by the quantity and quality of the available data, the type of studies published, the complexity of the outcome, and the availability and appropriateness of dose-response information. Because of this, OEHHA generally avoided a "one size fits all" approach, which would have been inefficient, robotic, and limiting. Rather, OEHHA used a more flexible and iterative approach, and adapted its evaluations to the particular strengths, weaknesses, and other characteristics of the available data on each individual outcome. Because of this, not all sections are organized the same, and differences will exist in how data are presented from one outcome to the next.

Comment 49: For lipid homeostasis in Appendix 7, "The relevant appendix/tables for lipids should come before the relevant appendix/tables for thyroid toxicity."

Response 49: The respective tables have been moved in response to this comment.

Comment 50: Regarding Appendix 7 (*Lipid Homeostasis*), "This is the only appendix for human epidemiological studies that provides detailed information about study quality. All other sections of Chapter 5 could benefit for this kind of analysis, especially the chapters on immunotoxicity, liver toxicity and developmental/reproductive toxicity."

Response 50: The tables on immunotoxicity, liver toxicity, developmental/reproductive toxicity, and cancer in Appendix 7 of the draft PHG document all provide similar information on study quality. This includes information on study design, sample size, study populations, selection procedures, participation rates, comparison groups, blinding, detection levels, distribution of exposure, exposure assessment, outcome assessment, confounding, magnitude of the association, probability findings are due to chance, dose-response, temporality, statistical issues, and others. As noted in the response to this reviewer's Comment 29, an additional table was created for the lipid studies because of the complexity and particular characteristics of these data.

Comment 51: Regarding Section 5.4.1 (*Recent Human Evidence*, *Thyroid Toxicity*), "*PFOA and thyroid hormone levels*: Please describe the study designs for these 19 results, and whether the conclusions differ for cross sectional vs prospective studies. This is only discussed for the 17 studies in older children but should be considered for all. Please also describe the magnitudes of these associations, regardless of statistical significance as well as sample size (statistical power could explain large but non significant effects). It is stated that study quality did not differ, but it should be clear whether the studies were of generally high or low quality."

Response 51: In response to this comment, information on the designs of these 19 studies is now provided in Section 5.4.1 of the draft PHG document. The fact that findings did not differ across the different designs is also now mentioned.

As described in the footnotes of Table A7.12 of the draft PHG document, associations that were above a particular magnitude are already identified. More detailed information on the magnitudes of these associations can be found in the publications themselves, which are fully referenced. This table also provides the sample sizes of each study.

It is now noted that studies varied greatly in terms of quality. Because of this, it cannot be stated generally whether these studies as a whole were of high or low quality.

Comment 52: "*PFOS and thyroid hormone levels*: Please add a call-out to Table A7.7, otherwise it appears that there are no separate appendix tables for PFOA and PFOS. The earlier comments regarding magnitudes of association, discussion of study design and quality, and sample size also apply here."

Response 52: A callout to this table (now labeled Table A7.12 in response to this reviewer's Comment 49) mentioning both PFOA and PFOS already appears in the introductory paragraph of Section 5.4.1 of the draft PHG document. In response to this comment, a call-out to this table has also been added to the part of Section 5.4.1 that focuses on PFOS. Study design, sample sizes, and several other features of study quality are already presented in Table A7.12. Extensive discussions of these studies (including the magnitudes of associations) were not presented because it was already clear from the information presented in Table A7.12 and in the summary that thyroid hormone levels would not be an appropriate outcome for health-protective concentration or PHG calculations. This is discussed in Section 5.4.4.

Comment 53: "Please add an appendix [Appendix 7] table for thyroid disease. It would be easier to understand and compare the specific study characteristics in a table, even if there are only four studies. Additionally, this section only summarizes the four identified studies, and does not make any comparison of their results. Please expand this section to discuss the consistency of findings and compare results across study populations and designs."

Response 53: OEHHA considered the reviewer's first comment here but has concluded that providing this table would add little to no benefit given the small number of studies and the fact that most of these involved different, and perhaps unrelated, types of thyroid disease. Given this small number, and the lack of replication for any given outcome, it was obvious that "thyroid diseases" would not be an appropriate outcome for health-protective concentration calculations. A table was not needed to make this conclusion. With regard to the reviewer's second comment here, a paragraph has been added to Section 5.4.1, under *Thyroid diseases*, providing an overall conclusion and discussing the consistency (or lack thereof) of these findings.

Comment 54: "Please describe [in Section 5.4.4] the magnitude of association for PFOA and TSH, and whether it might be of clinical concern."

Response 54: Thyroid physiology, with its multitude of clinical effects, complex feedback loops, and large degree of inter-individual variability, is incredibly complex (Miller et al., 2009). Because the data on PFOA and TSH were not as consistent or strong as those for other outcomes, they were not used to calculate health-protective concentrations. Because of this, an in-depth discussion of the complex relationship between TSH and clinical disease is well beyond the scope of this document.

Comment 55: "[Section 5.5.1] reports effect sizes more often than the others. This is helpful to visualize the magnitude of the effect but could probably be pared down to only select or representative associations."

Response 55: OEHHA has edited parts of this Section 5.5.1 to present a less detailed discussion.

Comment 56: Regarding pregnancy-related hypertension and preeclampsia in Section 5.5.1, "The two studies here are discussed at length, which may not be necessary since they do not contribute to the ADD. Most of this information could be presented in tables, with only the main findings and relevant characteristics summarized in this section. There are studies missing from the report on gestational hypertension. For example:

- Borghese, M.M., Walker, M., Helewa, M.E., Fraser, W.D., Arbuckle, T.E., 2020. Association of perfluoroalkyl substances with gestational hypertension and preeclampsia in the MIREC study. Environ. Int. 141, 105789.
- Rylander, L., Lindh, C.H., Hansson, S.R., Broberg, K., Kallen, K., 2020. Per- and polyfluoroalkyl substances in early pregnancy and risk for preeclampsia: a case control study in southern Sweden. Epub 2020/06/21 Toxics 8 (2). PubMed PMID: 32560030; PMCID: PMC7355444.

- Birukov, A., Andersen, L.B., Andersen, M.S., Nielsen, J.H., Nielsen, F., Kyhl, H.B., Jørgensen, J.S., Grandjean, P., Dechend, R., Jensen, T.K., 2021. Exposure to perfluoroalkyl substances and blood pressure in pregnancy among 1436 women from the Odense Child Cohort. Epub 2021/02/21 Environ. Int. 151, 106442. PubMed PMID: 33610053."

Response 56: In response to this comment, the studies cited by this reviewer and one additional study (Huo et al., 2020) were added to this section. The section was reorganized to only include summaries of important findings and relevant discussions.

Comment 57: "It is not clear why these few studies [on birth weight] were selected for detailed discussion out of the many in Table A7.15. Please describe the reasons for selecting these or expand the discussion to include others. Since there are many studies with conflicting results consider synthesizing results by performing a meta-analysis or reference published meta-analysis on this topic (Cao et al 2021, Gao et al 2021, Negri et al 2017)."

Response 57: These studies were selected because they provided either representative associations (as suggested by this reviewer in Comment 55) or they involved the most interesting, informative, or particularly important results. Importantly, all results are presented in Table A7.15 and readers are referred to this table multiple times throughout this Section 5.5.1. All results were considered in OEHHA's final conclusions.

OEHHA considered conducting a meta-analysis for select developmental and reproductive toxicity endpoints for PFOA and PFOS but ultimately determined that given the wide degree of heterogeneity in study designs, a meta-analysis would unlikely lead to different or more convincing conclusions than those already presented by OEHHA. For an effective meta-analysis, one would generally have to choose studies in which a number of aspects of study design were the same or similar. However, this was only the case for a subsample of studies. For example, for their meta-analysis of decreased birth weight, Cao et al. (2021) selected only 6 PFOA studies from dozens available (Table A7.15). Yet, the conclusion of the Cao et al. analysis ("no significant correlation") was similar that of OEHHA's analysis (Table 5.5.7). In summary, a meta-analysis would likely have to involve the exclusion of many studies, including some of potentially high quality, without any obvious improvement in overall clarity.

Comment 58: "The comments for the birth weight section also apply here [small for gestational age]."

Response 58: Detailed description of the cross-sectional study (Govarts et al., 2018) was removed. Only descriptions of cohort studies that found some associations remain included in this section. Importantly, all results are presented in Tables A7.15 and A7.16, and readers are referred to these tables throughout Section 5.5.1.

Comment 59: "Please summarize the results on puberty development by child sex. The report should also include studies on changes in sex hormone levels associated with PFOA/PFOS exposure."

Response 59: Only two studies examined associations of pubertal development with PFOA (Di Nisio et al., 2020; Ernst et al., 2019), and these studies had different experimental designs (one was cross-sectional and one was prospective cohort). Findings were somewhat inconclusive – delayed menarche in girls with high PFOA in Di Nisio et al. (2020) but no change in Ernst et al. (2019), although these studies cannot be directly compared in methodology. Overall, no significant associations for boys were reported with PFOA. Only one study analyzed pubertal development and PFOS (Ernst et al., 2019) and reported significant associations for boys and girls. Given the paucity of studies and even fewer results, a more generalized summary is not necessary.

Comment 60: "The review states that there are only four studies published up to date on woman's exposure to PFOA/PFOS and fertility or fecundity but there is one that was not included in either the EPA (2016) review or in this one:

- Lum KJ, Sundaram R, Barr DB, Louis TA, Buck Louis GM. Perfluoroalkyl chemicals, menstrual cycle length, and fecundity: Findings from a prospective pregnancy study. Epidemiology. 2017;28(1):90-8."

Response 60: In response to this comment, Lum et al. (2017) was added to Tables A7.19 and A7.20, and the text was changed to incorporate results from this study.

Comment 61: "All subsections [of Section 5.5.1] dedicate far more time to the strengths and weaknesses of individual studies than other sections do. This may not be necessary, unless the other sections will do the same. Discussion of possible bias/confounding should be moved to conclusions, and if a concern applies to only one study, it can be noted in the Appendix tables."

Response 61: In response to this comment, subsections of Section 5.5.1 have been revised to provide a more consistent level of detail throughout. Discussion of possible confounders throughout the section is limited to interstudy comparisons when trying to make sense of inconclusive or contradictory findings.

Comment 62: "The structure of the conclusions section [Section 5.5.4] should follow a similar structure of the conclusions in "Perturbation of Lipid Homeostasis". More specifically, there should be a summary of the study findings for the different outcomes, and a detailed discussion of possible confounders, study quality, and reasons for inconsistencies. A meta-analysis or coefficient plot would help synthesize the results from various cohorts on fetal growth."

Response 62: A detailed discussion and overall summaries of confounding and bias (which includes study quality and consistency) was provided in the conclusions (Section 5.3.4) for *Perturbation of Lipid Homeostasis* because this outcome was determined to be appropriate for ADD calculations. For the variety of reasons given throughout Section 5.5, reproductive outcomes were not selected for ADD calculations. Although

detailed analyses of bias, confounding, and quality were performed for developmental and reproductive outcomes, OEHHA determined it is most appropriate to present less detailed descriptions of these studies than those for lipid homeostasis.

Comment 63: Regarding Section 6.1.1, "The Faroe Islands NOAEC is much lower than the Abraham et al. (2020); NOAEC and OEHHA's BMD calculation (~4.75 ng/mL rather than 16-20 ng/mL). Reasons for this should be described. Is it because a 5% decrease was used (rather than 10%)? Please also describe why a 5% decrease in antibody levels would be used to calculate the BMD, when 10% was used in the other analysis, as well as how these differences should be interpreted."

Response 63: The choice of the benchmark response (e.g., 5% vs. 10%) was based on the principles presented by OEHHA's peer-reviewed guidelines in OEHHA (2008) and by the US EPA (2012), and this is now stated at the beginning of Section 6.1.1 in the draft PHG document. The exact reason why the Faroe Islands NOAEC is lower than the Abraham et al. (2020) NOAEC is unknown but could be related to chance or sample size. This is now stated in Section 6.1.1 of the draft PHG document.

Comment 64: "In the liver toxicity discussion [Section 6.1.1], Darrow et al. (2016) should not be described as a cross sectional study, when their exposure is modeled lifetime PFOA exposure. Table A7.5 also categorizes this study as a prospective cohort."

Response 64: In response to this comment, Darrow et al. (2016) is now described as a prospective cohort study in Section 6.1.1 and Table A7.5.

Comment 65: "For the ADD calculation, the choice to use the ALT NOAEC (9.8 ng/mL) rather than one of the lower values for immunotoxicity (BMD) is not well justified. There is an indication that the NOAEC may be lower than 9.8, even if the exact value is unknown. The animal study derived NOAEL should also be compared to the human NOAEC/BMD, and any differences or agreement between them should be discussed."

Response 65: The evidence linking PFOA to increased ALT and to vaccine response are both strong. However, the current literature on ALT has some particular strengths that makes it especially robust for risk assessment. These particular strengths are discussed in detail in Section 6.1.1 of the draft PHG document, but in response to this comment, are further reviewed in the same section (under a new heading labeled *Other*).

A common practice in risk assessment is to use high quality human data over animal data when they are available. This helps reduce the uncertainty associated with extrapolating findings from laboratory animals to humans. OEHHA's acceptable daily dose calculations are consistent with this standard practice.

Comment 66: "International regulations could also be included in Table 8.1, or discussed in the text."

Response 66: In response to this comment, several international regulatory standards are now mentioned in the Chapter 8 text under *Other Regulatory Standards and Advisory Levels*. The values (100-600 ppt) are much greater than those of US EPA, individual states or OEHHA's proposed PHGs because they are based on different studies and risk assessment methodologies.

DR. JAMIE DEWITT

Comment 1: "In reading the Attachment 2 and the Product, there did not appear to be additional subjects that were part of the scientific basis that were not described in the Product or Attachment 2. Taken as a whole, the Product and Attachment 2 appear to be based upon current and sound scientific knowledge, methods, and practices." [Note that this reviewer has defined "Product" as the draft PFOA and PFOS PHG technical support document.]

Response 1: OEHHA acknowledges the comment.

Comment 2: Regarding cancer as the primary adverse health affect associated with exposure to PFOA and PFOS, "It appears as if relevant subjects were included as part of the scientific basis for the proposed rule."

Response 2: OEHHA acknowledges the comment.

Comment 3: "A recently published critical review and meta-analysis of epidemiological literature for PFOA was not included in the Product. This study by Bartell and Vieira (2021) concluded that associations between PFOA and kidney cancer (and testicular cancer) were likely causal. While Bartell and Vieira (2021) did note that the number of studies was limited and that larger cohort studies were needed to support their conclusion, this critical review and meta-analysis should be included in the Product as a supporting study.

Bartell SM and Vieira VM. 2021.Critical review on PFOA, kidney cancer, and testicular cancer. J Air Waste Manag Assoc. 71:663-679."

Response 3: In response to this comment, this publication is now referenced in Section 5.7.1 of the draft PHG document, under *Kidney* cancer, and it is now noted that the authors' conclusions regarding causal inference are very similar to OEHHA's.

Comment 4: "It appears as if the proposed rule is based upon sound scientific knowledge, methods, and practices. Throughout the Product and ***Attachment 2***, rationale/justification for choices made appears to be transparent and complete. A particular strength of the Product and by extension, ***Attachment 2***, is in-depth analyses of the strengths and limitations of studies included in Chapters 5 and 6. Additionally, Chapters 7 and 8 contain clear descriptions and justifications for the choices made."

Response 4: OEHHA acknowledges the comment.

Comment 5: "One area of the Product and ***Attachment 2*** could be improved. The derivation of PHGs based on cancer and the proposed noncancer health-protective concentrations are based on the "most sensitive" health effects. However, neither the Product nor ***Attachment 2*** (or ***Attachment 1***, the Plain English Summary) define "most sensitive" with respect to health effects. As "most sensitive" could be interpreted in more

than one way, it is recommended that the operative definition for this phrase be included in a revised version of the Product and ***Attachment 2***."

Response 5: In the *Summary*, under *Derivation of the PHGs and HPCs*, the most sensitive effect is described as "occurring at the lowest dose." A sentence in Section 2.4 of the Methodology chapter was revised to indicate that the most sensitive effect occurs at the lowest dose.

Comment 6: "The Product considered seven human studies that included linkages between PFOA exposure and kidney cancer and when combined with animal and mechanistic data, OEHHA determined that these studies provided evidence that PFOA is a cause of kidney cancer. The (US EPA, 2021a) considered the quality of the Shearer et al. (2021) study to be of medium confidence and when combined with the remaining dataset of epidemiological, animal, and mechanistic studies, determined that the evidence was for a plausible linkage rather than a causal linkage. Therefore, the potential Federal carcinogenicity designation for PFOA may ultimately differ from the OEHHA designation."

Response 6: US EPA's rating of the Shearer study (Shearer et al., 2021) to be of medium confidence is based on US EPA's concerns regarding potential confounding (see Figure 123 in US EPA (2021a)). However, US EPA did not present a thorough, detailed, or quantitative analysis of confounding. As such, the underlying basis of these concerns is unknown.

OEHHA performed an extensive evaluation of Shearer et al. (2021) and found no major concerns regarding confounding. This is laid out in Section 6.2.1 of the draft PHG document.

One particular potential confounder mentioned by US EPA is socioeconomic status. However, while some studies have reported associations between lower socioeconomic status and higher rates of kidney cancer, this has not been seen in all studies (Aarts et al., 2010; Blake et al., 2017; Colli et al., 2009; Coughlin et al., 1997; Hu et al., 2003; Mellemgaard et al., 1994; Muscat et al., 1995; Semenza et al., 2001; Williams and Horm, 1977; Yuan et al., 1998). In fact, most evidence suggests that even if these associations are real, they are not strong enough to cause the elevated odds ratios seen in Shearer et al. (2021). Perhaps most importantly though, data from NHANES and other sources show that lower family income is associated with ***lower,*** not higher, serum PFOA concentrations (Nelson et al., 2012). As such, if any confounding by socioeconomic status did occur, it would have most likely biased the Shearer et al. (2021) results to the null and not towards the elevated odds ratios identified.

Overall, OEHHA determined the Shearer et al. (2021) study is of high quality and suitable as the critical study for derivation of the PHG.

Comment 7: "Section 6.2.2, which includes the cancer dose-response analyses for PFOS, discusses the level of evidence for PFOS carcinogenicity in detail. In this

section, data from studies of PFOA are used to support the conclusion that cancer is a sensitive endpoint for PFOS based on similarities in chemical structure and noncancer toxicity profiles for PFOA and PFOS. It is recommended that additional supporting data for similarities between PFOA and PFOS be included in this section in a revised version of the Product, i.e., similarities in modes and/or mechanisms of action. Additionally, it is unclear why the Shearer et al. (2021) study is not included in Section 5.7.1 on human evidence for PFOS as PFOS was one of the analytes measured in the Shearer et al. (2021) study."

Response 7: In response to this comment, Shearer et al. (2021) is now referenced in Section 5.7.1 on PFOS and cancer. It was already noted that the odds ratios for PFOS in Shearer et al. (2021) are no longer elevated after adjustment for PFOA (Section 6.2.1 of the draft PHG document). Additionally, a sentenced was added to section 6.2.2 indicating that PFOA and PFOS can both activate specific nuclear receptors. Other modes of action for PFOA and PFOS are not very well characterized.

Comment 8: "The intent of comparing the Product to the MCLG documents by the US EPA is not to indicate that one is "better" or "more correct" than the other but to point out inconsistencies between the two documents in terms of the assessment of the available science. In a revised version of the Product, it may be worthwhile to make note of the US EPA MCLG documents.

US EPA (2021a) Proposed approaches to the derivation of a draft maximum contaminant level goal for perfluorooctanoic acid (PFOA) in drinking water. External peer review draft. EPA Document No. 822D21001.

US EPA (2021b) Proposed approaches to the derivation of a draft maximum contaminant level goal for perfluorooctane sulfonic acid (PFOS) in drinking water. External peer review draft. EPA Document No. 822D21002."

Response 8: In response to this comment, the most recent draft US EPA MCLG documents (from 2023) were included in Chapter 8 of the second draft PHG document, and now in the final PHG document, and similarly the US EPA interim drinking water health advisory (HA) levels for PFOA and PFOS have been included in Table 8.1.

Comment 9: "Chapter 6 of the Product contains the dose-response assessment for the identification of points of departure (PODs) for derivation of the proposed noncancer health-protective concentrations. This Chapter contains detailed rationale/justification for the selection of specific PODs. Scientific judgment plays a key role in the process of health risk assessment, which can lead to differences in PODs and other values selected by groups of scientists performing the assessment(s). The detailed rationale/justification for the selection of specific PODs for noncancer health-protective concentrations makes it very clear that OEHHA has adequately addressed all important scientific issues relevant to each chemical and to the methods applied in the derivation of each health-protective concentration."

Response 9: OEHHA acknowledges the comment.

Comment 10: "An epidemiological study by Li et al. (2022) just published may be informative for PFOS. It concerns kidney cancer and the study population is exposed to a mixture of PFAS that appear to be dominated by PFOS and one other PFAS. Otherwise, it does not appear as if relevant studies useful for assessing dose response relationships or otherwise informing the PHG development were missed."

Response 10: In response to this comment, the Li et al. (2022) study is now discussed under *Other studies* in Section 5.7.1 of the draft PHG document.

Comment 11: "Within the Product and ***Attachment 2***, the only specific mention of 'sensitive populations' is in the Populations definition for PECO criteria. ***Attachment 1***, the Plain English Summary, does include the statement: 'The PHGs and noncancer health-protective concentrations are based on comprehensive analyses of information on the toxicology of each compound and include consideration of sensitive populations, such as infants and children.' However, it does not appear as if a similar statement is explicitly included in the Product or ***Attachment 2***.

In a revised version of the Product and ***Attachment 2***, it is recommended that sensitive populations be defined and that a rationale for why the chosen PHGs will be health protective of identified sensitive populations."

Response 11: In response to this comment, a sentence in the *Summary* has been modified to indicate that the proposed PHGs are based on the most sensitive health effects and include consideration of sensitive populations, such as infants and children. While infants and children were determined not to be more sensitive to the carcinogenic effects of PFOA and PFOS, an intraspecies uncertainty factor of $\sqrt{10}$ was applied to the noncancer HPCs to account for the lack of data on children in the critical studies. Furthermore, the HPCs and PHGs were derived using lifetime weighted drinking water intake rates that incorporate the higher intake rates for infants and young children, on a per body weight basis, when compared to adults. In these ways, OEHHA has accounted for these sensitive populations and rationale is provided in sections of the document where these parameters are applied.

DR. JENNIFER SCHLEZINGER

Comment 1: In Section 4.1, "I would not include the PFOA half-life estimate in female mice, repeatedly dosed with PFOA (from Lou et al., 2009). The estimate is questioned as 'contradictory' in the original paper, and there is no support for a 1.2d half-life for PFOA in other publications."

"I also question the comparison of rat PFOA pharmacokinetic data with other species. The rat is an outlier in terms of having strong sex differences in elimination. Although, I agree that the sex difference in rat PFOA half lives did reveal an interesting transporter protein-based mechanism."

Response 1: Table 4.1.1 is meant as a general review of all available data. Since toxicity studies from rats, as well as mice, are presented and discussed in Section 5, PFOA toxicokinetics in both rats and mice are presented in Section 4.1. Specifically, comparisons with other species are made, since the ultimate steps of this risk assessment include interspecies extrapolation of toxicity values to derive a human acceptable daily dose. In response to this comment, footnote a to Table 4.1.1 has been edited to indicate the authors of the original study (Lou et al., 2009) noted their one-compartment model fit the repeated dose data only when the half-life was reduced from 15 to 1.2 days.

Comment 2: In Section 4.2, "Human data from the clinical trial reported in the Convertino study (2018) should not be considered. The people in the study were extremely ill with confounding underlying pathology that negates comparison to healthy people.

Also note: Data from the same clinical trial reported in Convertino, 2018 were used in the human half-life estimate in Dourson, 2019 and appears to be included in the human PFOA half-life estimate in Table 4.7.1. Again, I argue that data/estimates from that study are highly confounded by underlying pathology and should NOT be used in estimating PFOA half-life in healthy people."

Response 2: OEHHA agrees that the human data from the clinical trial reported by Convertino et al. (2018) should not be used for PFOA half-life derivation. The PFOA half-life estimate adopted in this document did not rely on Convertino et al. (2018) data for a number of reasons, including the fact highlighted by this reviewer that the dataset was not derived from observations in healthy individuals.

Comment 3: In Section 4.2, "I concur with the assessment that Trudel, 2008 should not be used in the estimate human absorption."

Response 3: OEHHA acknowledges the comment.

Comment 4: In Section 4.2, "A critical point not considered with regard to dermal absorption of PFOA and PFOS is their ionizability. These chemicals will be ionized at

physiological pH. Dermal absorption occurs only via diffusion and thus would be limited for an ionized chemical. This was shown by Franko et al., 2012."

Response 4: In response to this comment, the observation that dermal absorption of PFOA is somewhat limited at physiological pH due their likely ionized state was added to Section 4.2 and Franko et al. (2012) was cited.

Comment 5: In Section 4.2, "The one animal inhalation study in an animal model that I found (Hinderliter (2003)) was included in this analysis. There is evidence in humans (particularly in occupational exposures) to support the conclusion that inhalation exposure can lead to absorption in PFOA. Little is known about this route of exposure, however."

Response 5: OEHHA acknowledges the comment.

Comment 6: In Section 4.3, "I do not understand the point is being made with the following statement, 'However, in a cross-sectional study of 300 children in Texas, plasma concentrations of PFOA or PFOS steadily increased for 0-3, 3-6, 6-9 and 9-13 years of age groups, indicating that a possible early life spike in plasma concentrations would have dissipated by 3 years of age (Schecter et al., 2012).' The study cited shows that multiple PFAS continue to increase in blood concentration up to the oldest age group, so I do not see how this supports dissipation of an 'early life spike.'"

Response 6: The paragraph in Section 4.3 that precedes the one referred to in this comment describes several studies that observed very high concentrations (a "spike") of PFOA or PFOS at 12-18 months of age, which were about four-fold higher than the adult (maternal) values. Presumably, this early life peak would dissipate with time, even with constant PFOA/PFOS exposure, resulting in more adult-like PFOA/PFOS values when the infants grow up. However, Schecter et al. (2012) did not observe any decreasing trends in PFOA or PFOS levels in 0-3, 3-6, 6-9 and 9-13 years of age groups, and to the contrary, the PFOA and PFOS plasma concentrations increased with age. The observation that levels in the 0-3 years of age group of this study were not higher than those of other groups, and presumably not higher than adult levels would indicate that the early-life spike, observed at 11-18 months would have a minor effect when averaged over 0-3 years of life, and therefore, would have likely dissipated by age 3, at least as interpreted in light of the Schecter et al. (2012) data.

Comment 7: In Section 4.3, "I do not think that data support the following statement, 'Displacement of endogenous ligands from carrier or transporter proteins has been hypothesized as one of the possible mechanisms of action in PFOA/PFOS toxicity.' The mass balance between fatty acids and PFAS is more likely to displace PFAS from shared binding proteins than the other way around."

Response 7: Regarding liver fatty acid binding protein (L-FABP), Luebker et al. (2002) notes that "this work provides evidence to support the hypothesis that displacement of

endogenous ligands from L-FABP may contribute to toxicity in rodents fed these fluorochemicals."

Comment 8: In Section 4.3, "The following is an overstatement, 'At physiological pH, PFOA and PFOS are charged and therefore, would not be able to cross membranes via passive transport.' First, diffusion is limited but does occur (Kimura et al., 2017). Second, there are portions of the GI tract with pHs below the pKa of PFOA and PFOS (e.g., stomach and upper small intestine). I do agree that active transport is the major mechanism of movement across membranes."

Response 8: Physiological pH is 7.35-7.45. In Comment 4, this reviewer notes, "These chemicals will be ionized at physiological pH."

Kimura et al. (2017) observed decreased uptake of PFOA into Caco-2 cells in the presence of several transporter inhibitors. The study did not provide evidence that the remaining uptake was due to passive diffusion. The remaining uptake could be due to less than 100% inhibition, and additional unknown or transporters not considered could be involved.

To avoid confusion, the corresponding text was changed to "PFOA and PFOS … would have limited ability to cross membranes via passive transport."

Comment 9: In Section 4.4, "I agree; PFOA and PFOS are inert to biotransformation."

Response 9: OEHHA acknowledges the comment.

Comment 10: "The following introduction [in Section 4.5] is not consistent with the data presented:

'Excretion pathways of PFOA and PFOS include:

1) Renal or urinary excretion, which occurs in all mammalian species and appears to be dominant in fast eliminators, e.g., in the case of PFOA elimination in the female rat.
2) Fecal or gastrointestinal excretion appears to play a more important role in slow eliminators, such as humans; likely subject to enterohepatic circulation.
3) Elimination pathways via pregnancy and lactation in human females (Wong et al., 2014).'

Renal/urinary and biliary/fecal excretion occur in all mammals (see Hundley et al., 2006)

Urinary excretion is dominant in humans, in spite of the fact that the biliary clearance rate is higher than the urinary clearance rate. Enterohepatic recirculation limits actual excretion in feces.

Elimination pathways in human females include menstruation, pregnancy and lactation. While Table 4.5.2 suggests that menstruation may play a lesser role in elimination than lactation, studies do show that oral contraceptive use is associated with increased PFOA and PFOS concentrations (e.g., Ngueta et al., 2017)."

Response 10: OEHHA agrees with the statement that renal/urinary and biliary/fecal excretion occur in all mammals. The cited excerpt from the draft does not contradict it.

The following considerations, based on discussion in the PHG draft document, indicate that urinary excretion may not be the dominant elimination pathway in humans.

Table 4.5.1 lists the published estimates of human urinary clearance for PFOA and PFOS. For PFOA, excluding the 0.79 ml/kg-day estimate from Zhang et al. (2013b), which is over 10-fold higher than other estimates, the geometric mean of the remaining estimates is 0.086 ml/kg-day, which constitutes approximately 31% of the total PFOA clearance estimate (2.8×10^{-4} L/kg-day) used in deriving the proposed HPCs. For PFOS, the geometric mean of the urinary clearance estimates from Table 4.5.1 is 0.0239 ml/kg-day, which constitutes approximately 6% of the total PFOS clearance estimate (3.9×10^{-4} L/kg-day) used in deriving the proposed HPCs. This suggests that urinary clearance is not the dominant excretion pathway in humans. Rather, fecal clearance which is the only other significant route appears to "play a more important role," as stated in the draft.

In response to this comment, elimination pathways in human females were amended to include menstruation.

Comment 11: For Section 5.1, "More human studies have been published supporting a relationship between PFAS and adverse immune endpoints. Two more studies show a decrease in antibody response to vaccination, supporting already strong evidence. Confidence for increased risk of infectious disease was considered 'low' by NTP in 2016. But four new studies have been published that likely increase confidence in this endpoint."

Table 1 [from reviewer's comment]: PFAS and immunotoxicity endpoints.

Study	Endpoint	Association
Reduced antibody response		
(Shih et al., 2021)	Serum antibody concentrations against hepatitis type A and B in adults	PFAS concentrations at 14, 22 and 28 years of age
(Abraham et al., 2020)	Reduced antibody response to vaccinations for Haemophilus influenza	PFOA level in serum of children NOAECs: 12.2, 16.9 and 16.2 µg/L

	type b, tetanus and diphtheria	
Increased risk of infectious disease		
(Wang et al., 2022)	Diarrhea in infant	PFAS in maternal serum
(Ji et al., 2021)	Increased risk of SARS-CoV2 infection in adults	Urinary PFAS
(Bulka et al., 2021)	Increased pathogen (cytomegalovirus, Epstein Barr virus, hepatitis C and E, herpes simplex 1 and 2, HIV, T. gondii, and Toxocara spp) burden score	Serum PFAS, particularly in adolescents
(Dalsager et al., 2021)	Increase in the risk of hospitalization due to any infection	PFOS in maternal serum
Other immune endpoints		
(Salihovic et al., 2020)	Reduced serum inflammatory proteins	PFAS in serum of elderly

Response 11: The studies by Abraham et al. (2020) were discussed at the end of Section 5.1.1 of the draft PHG document; Bulka et al. (2021), Dalsager et al. (2021), and Salihovic et al. (2020) were included in Table A7.29 of the draft PHG document. In response to this comment, the other studies (Ji et al., 2021; Shih et al., 2021; Wang et al., 2022) have been added to Table A7.29. In general, the results of these newer studies support OEHHA's conclusions regarding PFOA and PFOS and immunotoxicity.

Comment 12: "Allergy and autoimmunity are a different type of immune dysfunction (than ability to fight infection). I am thus not surprised that strong associations have not necessarily been found between PFOA/PFOS exposure and increased risk of allergy, delayed type hypersensitivity or autoimmune disease."

Response 12: OEHHA acknowledges the comment.

Comment 13: "Dr. Jamie DeWitt's studies, in particular, have consistently shown a reduction in antibody response to SRBCs in animal models, supporting the cause-and effect relationship between PFOA/PFOS exposure and reduced antibody response to vaccination in humans. An important study also to consider is Guruge et al., 2009, which showed a significant reduction in survival of influenza a infection, following 21 day exposure to PFOS (LOAEL 0.005 mg/kg/day; 189 ng PFOS/ml serum). A recent study showed that a 28 day PFOS exposure to 0.0015 mg/kg/day (99 ng PFOS/ml serum) modified distributions of immune cell types and resulted in greater weight loss in response to influenza a infection (Torres et al., 2021)."

Response 13: Detailed analysis of animal evidence was not included given the already large size of the document and its primary focus on human studies for dose-response analysis. Relevant studies from the DeWitt group are included in Table 5.1.5.

OEHHA did not independently analyze animal studies prior to 2016 but relied on the comprehensive NTP (2016) review, which considered Guruge et al. (2009) in its identification of PFOS as "an immune hazard to humans."

In response to this comment, Torres et al. (2021) has been added to Table 5.1.6.

Comment 14: "I agree that the relationship between PFAS exposure and suppressed immune responses is well supported by animal and human data. The data suggesting associations between PFAS exposure and inappropriate activation of the immune system (allergy and autoimmunity) is not strong."

Response 14: OEHHA acknowledges the comment.

Comment 15: "Overall, the analysis [of liver toxicity] is thorough. However, it does not address a critical criticism of studies of PFOA/PFOS liver toxicity in rodent models. Adverse effects in liver are most certainly an outcome of PPARa activation (among other mechanisms), and there are species differences in rodent and human PPARa. This is not to say that humans are not susceptible to PFAS-induced effects that are mediated by PPARa. I suggest that a specific section be added that addresses this issue head on. There are two in vivo studies in mice expressing human PPARa that need to be called out. Nakagawa et al., 2012 shows that hPPARa mice respond to PFOA with increased liver weight, liver triglycerides and plasma Alt. Schlezinger et al., 2021 shows that hPPARa mice respond to PFOA with increased liver weight and liver triglycerides, as well as with increased expression of genes whose expression is controlled by PPAR. It less likely that hPPARa plays a significant role in the liver toxicity induced by PFOS, however, as shown recently in the hPPARa mouse model (Su *et al*., 2022)."

Response 15: The relevant PPARα discussion was in Section 5.7.3 (*Mode of Action and Mechanistic Considerations*) of the draft PHG document. In response to this comment, it has been moved into a newly created Section 5.2.4, *Role of PPARα in Liver Toxicity*. Descriptions of Nakagawa et al. (2012), Schlezinger et al. (2021) and Su et al. (2022) were added to the discussion. An additional transgenic study (Schlezinger et al., 2020) has also been added.

Comment 16: Regarding liver toxicity, "Further, there is ample evidence in human hepatocyte models, including primary human hepatocytes and liver spheroids, for induction of PPARα, CAR and PXR target gene expression by PFOA and PFOS (Wolf *et al*., 2008; Bjork *et al*., 2011; Wolf *et al*., 2012; Buhrke *et al*., 2013; Peng *et al*., 2013; Rosen *et al*., 2013; Buhrke *et al*., 2015; Behr *et al*., 2019; Rowan-Carroll et al., 2021)."

Response 16: Section 5.7.3 of the draft PHG document mentions proposed CAR- and PXR-mediated mechanisms of PFOA and PFOS toxicity, specifically in the context of carcinogenicity, citing among others, multiple papers by Rosen and colleagues. In response to this comment, the additional papers cited by the commenter have been added to the PHG document.

Comment 17: "Overall, the data strongly support that human liver is a target organ of PFOA and PFOS."

Response 17: OEHHA acknowledges the comment.

Comment 18: In Section 5.3, "Great care needs to be taken in interpreting effects of PFOA and PFOS on serum lipids (triglycerides and cholesterol) in animal models. And the following is an overinterpretation of the data presented:

Pg. 108, 'In contrast, some animal studies have shown decreased cholesterol with PFOA and PFOS exposure (Table 5.3.6). Different results in animals and humans may be explained by the stronger activity of PPARα in animals, which is involved in the metabolism of cholesterol and fatty acids.'

First, studies that do NOT report serum PFAS concentrations should not be considered. Second, experimental exposures that result in supra-human serum concentrations should not be considered. It is becoming clear that PFOA, at least, induces a non-monotonic dose response with regard to effects on serum lipids, with increases in serum lipids being observed at low PFOA serum concentrations and decreases in serum lipids being observed at high (non-human-relevant) serum concentrations, likely a result of the increasing influence of PPARa activity. Studies that support this are outlined below."

Response 18: The citation from the PHG draft refers only to cholesterol, not all lipids. The basis for the hypothetical mechanism, in which lower doses to laboratory animals would result in increased serum cholesterol, while higher doses would result in decreased cholesterol, is not clear. In fact, the only study among those listed in Table 5.3.1 that shows increased serum cholesterol is Rebholz et al. (2016), at the relatively high level of 3.5 mg/kg-day (26.9 µg/ml in serum in males), while much more sensitive studies (NTP, 2019a; Pouwer et al., 2019) reported decreased serum cholesterol at serum PFOA concentrations as low as 0.378 µg/ml. Comment 20 below cites several PPARα transgenic studies (human PPARα in mice) that demonstrated increased serum cholesterol at lower doses. These mechanistic studies support OEHHA's conclusion that species differences in cholesterol effects may be explained by PPARα genotype. Such studies have a mechanistic and not strictly toxicological premise, and they were not included in Table 5.3.1.

The studies outlined in Comment 19 below refer to serum triglycerides, and not cholesterol. Triglyceride effects are discussed separately from cholesterol effects in the draft PHG document, and this discussion takes consideration of data inconsistencies.

Comment 19: Regarding serum triglycerides in Section 5.3, “In male mice, studies have reported that perfluorocarboxylic acids induced both increases (S E Loveless et al., 2006; Minata et al., 2010; Yan et al., 2014) and decreases in serum TG (S E Loveless et al., 2006; Minata et al., 2010; Pouwer et al., 2019; Qazi et al., 2010; Wang et al., 2015; Xie et al., 2003; Yan et al., 2014) or had no effect (Nakamura et al., 2009; Pouwer et al., 2019). In studies with male rats, perfluorocarboxylic acid exposure also was associated with decreased serum TG (Elcombe et al., 2010; Haughom & Spydevold, 1992; Kudo et al., 1999; S E Loveless et al., 2006; Scott E Loveless et al., 2008; NTP, 2019), increased serum TG (NTP, 2019; Zhang et al., 2008), or no effect on serum TG (NTP, 2019). There are two mouse studies that are important to note, in which full dose response assessments were conducted and serum PFOA concentrations were measured (Pouwer et al., 2019; Yan et al., 2014). Across these two studies, at lower PFOA body burdens, increased serum triglycerides were observed and at high PFOA body burdens (above those measured even in fluorochemical workers in the US), decreased serum triglycerides were observed. Furthermore, in a study with male cynomolgus monkeys, significant increases in serum triglycerides were observed following exposure to PFOA at serum levels less than 90 µg/mL (Butenhoff et al., 2002). Thus, when only studies that used exposure scenarios resulting in human-relevant serum PFOA levels are considered, PFOA exposure consistently results in increased serum triglycerides.”

Response 19 OEHHA acknowledges the comment that PFOA effects on triglycerides (TG) are varied. However, the draft PHG document does not make any statement on the direction of this effect and acknowledges recent animal studies that reported TG increases or decreases (Section 5.3.4).

The sentences in Section 5.3.4 cited in Comment 18 refer to cholesterol, and not triglycerides. In fact, most animal studies evaluated in this draft or published prior to 2016 and evaluated elsewhere (US EPA, 2016a) reported decreased plasma or serum cholesterol. Overall, PFOA/PFOS effects on cholesterol in animal studies appear to be more consistent than effects on TGs.

Comment 20: “Studying cholesterol biology in rodents has several challenges. Diet influences serum cholesterol levels (Dietschy et al., 1993). Cholesterol homeostasis differs depending on mouse strain and sex (Bruell et al., 1962). Species differ in the distribution of cholesterol among the different cholesterol particle types (Yin et al., 2012). However, with careful model and experimental design, these challenges can be addressed.

Studies using rodents fed a standard, low fat/low cholesterol rodent diet and exposed to PFOA for 6 weeks show decreased serum cholesterol levels (reviewed in Rebholz et al. (2016)). However, when mice are fed a cholesterol and fat-containing diet, PFOA does increase serum cholesterol levels (Rebholz et al., 2016), particularly in males and in C57BL/6 mice at a serum concentration of approximately 30 µg PFOA/mL. In a dose response analysis in male APOE*3-Leiden.CETP mice treated with PFOA for 4 weeks, serum cholesterol concentrations were only decreased in mice with a PFOA serum

concentration of 144 µg/mL (Pouwer et al., 2019). Importantly, in mice expressing human PPARα, PFOA increased serum cholesterol. Nakamura et al. (Nakamura et al., 2009) exposed male hPPARα (Sv/129 strain) to 0.3 mg PFOA/kg/day for 2 weeks (no serum PFOA concentration was reported) and Schlezinger et al. (J. Schlezinger et al., 202[1]; Schlezinger et al., 2020) exposed male hPPARα mice to 0.7 mg PFOA/kg/day for 6 weeks (47 µg PFOA/mL serum). In both studies, PFOA exposure was associated with increased serum cholesterol, particularly low density lipoprotein cholesterol (Nakamura et al., 2009; J. Schlezinger et al., 202[1]; J. J.Schlezinger et al., 2020). No study in rodents to date has investigated the relationship of PFAS at steady state exposures to effects on serum lipids; however, increased serum cholesterol with associated with serum PFAS concentrations in household cats (Weiss et al., 2021). When studies used human-relevant diets and exposure scenarios, PFOA exposure consistently results in increased serum cholesterol in sensitive rodent strains, including one that expresses human PPARα."

Response 20: OEHHA acknowledges the comment. In response to this comment, the transgenic studies by Nakamura et al. (2009) and Schlezinger et al. (2020, 2021) are now described in Section 5.2.4 (*Role of PPARα in Liver Toxicity*, see Response 22 below).

Comment 21: Regarding mechanisms of action for lipid effects, "I reiterate that the PFAS-induced effects are likely a result of the actions of PFAS in the liver. Thus, regulators need to be aware that species differences in PPARa are likely to be important. With that said, evidence discussed above with regard to liver toxicity, also supports the ability of PFOA and PFOS to perturb serum lipids via alterations in signaling in the liver in a human-relevant manner."

Response 21: OEHHA acknowledges the comment. Section 5.2.4, *Role of PPARα in Liver Toxicity*, has now been added, which discusses available mechanistic evidence in detail and presents conclusions regarding the human relevance of observed liver and lipid effects.

Comment 22: Regarding Section 5.3, "Overall, the human epidemiological data and data derived from animal models that are human relevant in dose and diet strongly support the association between PFAS exposure and dyslipidemia. Further, data from the humanized PPARα mouse model also support the association."

Response 22: OEHHA acknowledges the comment. The newly added PPARα section (Section 5.2.4) reviews relevant findings in the humanized PPARα mouse model.

Comment 23: Regarding thyroid toxicity, "Overall, the results from the human epidemiology do not show a strong or consistent association between PFOA and/or PFOS in increased TSH, which is used for clinical diagnosis of hypothyroidism. I am concerned that the table with the results from the NTP study in rats does not include serum PFOS concentrations. Studies in rats are fairly consistent in showing negative associations between PFOA and PFOS exposure and decreases in T3 and T4, but they

are not accompanied by increases in TSH. Thus, it is hard to determine the biological significance of the observations. The evidence is strong that PFAS can bind to TTR, which could reduce serum hormone levels. But, it is not clear that these effects are occurring at human-relevant PFAS serum concentrations."

Response 23: Table 5.4.2 describes effects from PFOA exposure, and not PFOS. In response to this comment, serum PFOA concentrations have been added to Table 5.4.2 that summarizes the thyroid toxicity findings in the NTP (2019, 2020) studies of PFOA in rats. The PFOS results are described in the narrative, and plasma concentrations have been added.

Hypothyroidism is not the only manifestation associated with thyroid toxicity. In hypothyroxinemia, low thyroxine (T4) is not accompanied by a compensatory increase in TSH. Maternal hypothyroxinemia can spontaneously occur in human pregnancy and has been linked to developmental and cognitive delays in offspring (Negro et al., 2011). Thus, decreases in T4/triiodothyronine (T3) can constitute an adverse effect even without increased TSH.

Regarding the mechanism of PFAS binding to transthyretin (TTR), Table A6.2 lists available K_d estimates measured in in vitro systems using human cells, which range 60×10^{-9} – 10^{-6} M. At the low end estimate, PFOA at a concentration of 25 ng/ml (60×10^{-9} M), which is about 10-fold higher than currently observed background levels in the US but equal to or lower than serum levels in contaminated areas, would be able to displace half of TTR binding sites. However, thyroid toxicity studies were not used or considered for ADD calculation, and no specific claims were made on the relevance of animal findings to human health.

Comment 24: "On pg. 118, it states, 'Preeclampsia is a condition in which the pregnant woman is hypertensive because of reduced renal excretion associated with a decrease in GFR (US EPA, 2016b).' This is not correct. Preeclampsia is a disease of the placenta (Rana et al., 2019)."

Response 24: In response to this comment, clarification has been added in Section 5.5.1 to indicate that the placenta appears to be central to the pathogenesis of preeclampsia.

Comment 25: "I agree that epidemiological data support and association between PFOA and PFOS exposure and increased risk of hypertensive disorders of pregnancy. The strength of the association is limited as results across studies remain inconsistent, particularly for gestational hypertension. I also agree that the results are inconclusive for fetal growth, pubertal development and fertility/fecundity for humans."

Response 25: OEHHA acknowledges the comment.

Comment 26: "An important developmental endpoint in humans does not appear to have been considered, which is bone quality. Analyses of early life exposure to PFAS,

including PFOA and PFOS, are consistently associated with reductions in bone quality in childhood, adolescence and early adulthood (Buck Louis et al., 2018; Buckley et al., 2021; Cluett et al., 2019; Di Nisio et al., 2020; Jeddy et al., 2018; Khalil et al., 2018). This endpoint is important, in particular, for three reasons. 1) PFAS have been found in human bone (Koskela et al., 2017). 2) Reduced ossification in rodent pups exposed in utero (Lau et al., 2006) is the endpoint used for the candidate RfD for PFOA (https://www.federalregister.gov/documents/2020/03/10/2020-04145/announcement-of-preliminary-regulatory-determinations-for-contaminants-on-the-fourth-drinking-water). 3) Failure to reach peak bone mass in early adulthood is a significant risk factor, and perhaps the most important factor, in determining osteoporosis risk (Hui et al., 1990; Klibanski et al., 2001).

Results from animal studies strongly support a cause/effect relationship between PFOA and PFOS exposure and adverse developmental and reproductive health outcomes. First, the analysis of recently published studies includes two that support bone as a target organ of early life exposure to PFOA (Koskela et al., 2016; van Esterik et al., 2016). Second, a newer experimental study and a meta-analysis continue to support that conclusion that PFOA is a male, reproductive, developmental toxicant, which leads to disruption of testis function and testosterone production (Bao et al., 2021; Wang et al., 2021). Fewer studies have investigated the effects of PFOS on male reproductive development, but effects seem to be similar to PFOA. In females, the data support the conclusion that PFOA and PFOS are placental toxicants, including newer studies (Jiang et al., 2020; Li et al., 2022; Li et al., 2021; Wan et al., 2020).”

“Bone (developmental toxicity), placenta (reproductive toxicity) and testis (developmental and reproductive toxicity appear to be important target organs for PFAS.”

“Overall, effects on bone should be included in the epidemiological and animal model analyses and conclusions.”

Response 26: OEHHA agrees that there is evidence from epidemiologic studies that PFOS and PFOA adversely affect bone health. However, this evidence is less robust than that for cancer, lipid homeostasis, or hepatotoxicity, the outcomes OEHHA used to calculate its health-protective concentrations. A particular weakness in the studies cited by the reviewer is the overall lack of information needed to accurately assess dose-response relationships. For example, several of the studies mentioned by the reviewer present results only as regression coefficients where the exposure variable (PFOS or PFOA in this case) is logarithmically transformed (Buck Louis et al., 2018; Cluett et al., 2019; Buckley et al., 2021). Estimating dose-response relationships using these types of effect measures would require assumptions that would be difficult to support without further information. Categorical analyses, plots of individual data, the impact of outlying values, or model fit parameters were generally not provided.

Another common problem with these studies is the possibility of confounding by other PFAS. In several of these studies, associations were not only seen for PFOA or PFOS,

but also for other PFAS (Buck Louis et al., 2018; Cluett et al., 2019; Khalil et al., 2018; Jeddy et al., 2018; Buckley et al., 2021). In many instances, the effect sizes for these other PFAS were similar to, or even larger than those seen for PFOS or PFOA. Analyses attempting to separate out the effects of the different PFAS were either not presented or resulted in somewhat conflicting results. For example, in Cluett et al. (2019), PFOA showed by far the strongest association with decreased bone mineral density (BMD) when entered into the linear regression models by itself (that is, without other PFAS in the same model) (Cluett et al., 2019). However, in the weighted quantile sum regression model that included multiple PFAS, a different PFAS, perfluorodecanoate, received a much greater weight than PFOA. Overall, an important weakness in several of the studies of PFAS and bone health is the difficulty in separating out the effects of PFOA and PFOS from other PFAS.

Other significant weaknesses in the studies cited by the reviewer include inadequate statistical power (Khalil et al., 2018), multiple comparisons issues (Buck Louis et al., 2018), ecologic exposure data (Di Nisio et al., 2020), and questions regarding generalizability (Khalil et al., 2018).

There are also several studies not mentioned by the reviewer that have examined PFAS and bone health (Banjabi et al., 2020; Hu et al., 2019; Khalil et al., 2016; Lin et al., 2014; ATSDR, 2021). However, most of these also suffer from weaknesses that preclude their use in estimating dose-response. For example, using data on participants ages 12 years and older from the 2009-10 NHANES, Khalil et al. (2016) identified an inverse association between serum concentrations of PFOS and total femur BMD (Khalil et al., 2016). However, similar associations were also seen for PFOA, PFHxS, and PFNA. In addition, while categorical analyses were presented, the category means or cut-off points were not provided. As such, these data cannot be used to assess dose-response. In another study, this one using data from the 2005-08 NHANES, PFOS was also linked to decreased BMD (Lin et al., 2014). Again, exposure category means or cut-off points were not provided. In addition, the dose-response relationship between PFOS and BMD had a somewhat unusual shape (an inverted-u shape). This is something for which further investigation and clarification would be needed before these findings could be used to develop a PHG.

Overall, while there is fairly extensive animal, mechanistic, and human evidence linking PFAS to bone health (Kirk et al., 2021; US EPA, 2016a, 2016b; ATSDR, 2021), the issues discussed above raise important concerns about their use for PHG development at this time. A sentence has been added to Section 5.5 (*Developmental and Reproductive Toxicity*) to acknowledge the evidence linking PFOA and PFOS to adverse effects on bone health.

Comment 27: Section 5.5: “I was surprised to see that activation of nuclear receptors beyond PPARγ. (i.e., PPARα, CAR and PXR) received little attention as mechanisms of action for developmental and reproductive toxicity. Although, after from searching on PubMed, this seems to be a result of the state of the science.”

Response 27: OEHHA acknowledges the comment.

Comment 28: "The data on the potential neurotoxicity of PFOA and PFOS are very limited. In Guo et al. (2019), it appears that the effect on protein expression the brain occurs downstream of effects in the liver. Given that there was significant weight loss in the mice with this effect (and the serum level of PFOA was at a high occupational level), it is unclear if the effect is specific to the brain or just a downstream result of overt toxicity."

Response 28: In response to this comment, the mention of decreased body weight and possible involvement of overt toxicity for effects observed at high dose in Guo et al. (2019) was added.

Comment 29: "I concur that the strongest epidemiological evidence for PFOA-induced cancer is for kidney and testicular cancers. It is important to point out that there also is evidence of non-cancer endpoint related effects in testis, which point to testis as a sensitive target organ of PFAS. These target organs were supported in a recent meta-analysis, as well (Bartell and Vieira, 2021). The epidemiological evidence of increased risk of pancreatic cancer is limited because this is a rare cancer, but should not be dismissed because of the very low survival rate and the strong evidence of pancreatic cancer in animals studies. Confirmation of risk of breast and liver cancer needs to be generated from studies of more cohorts. There does not appear to be epidemiological evidence to support prostate as a target organ for cancer induction."

Response 29: The Bartell and Vieira (2021) meta-analysis is now included in Section 5.7.1, under *Testicular cancer*. With regard to pancreatic cancer, OEHHA agrees with the reviewer and now notes that a causal relationship between PFOA and pancreatic cancer cannot be ruled out at this time (Section 5.7.1, *Pancreatic cancer*). With regard to breast cancer and liver cancer, the reviewer may be correct. However, making definitive statements regarding future research priorities or "needs" is beyond the scope of this particular document. Finally, OEHHA agrees with the reviewer's comment regarding prostate cancer, and OEHHA's current conclusions regarding this cancer are consistent with the reviewer's comment.

Comment 30: "I concur that there is significant, multi-study evidence [in laboratory animals] of liver and pancreatic tumors induced by PFOA and PFOS and testicular cancer induced by PFOA. A single study showing increased risk of uterine tumors induced by PFOA is insufficient to make conclusions. I have two concerns with the analysis, however. First, where serum PFAS data are provided, it is clear that carcinogenesis only occurs are concentrations that are not experienced by humans. Second, no studies of humanized PPARa mice appear to have been included, see below."

Response 30: Animal carcinogenicity bioassays typically are conducted at higher doses due to the relatively small sample sizes. Furthermore, evidence from the

epidemiology studies indicate that environmental levels of PFOA in some locations have increased the risk of renal cell cancer.

Humanized PPARα mouse studies have not been included in the discussion of the cancer mode of action (Section 5.7.3) because none investigated carcinogenesis.

Comment 31: "Human PPARα is less responsive to PFOA than rodent PPARa (Nakamura et al., 2009), and the human PPARα response to PFOS is even less efficacious (Su et al., 2022). This is also evident in vitro (Nielsen et al., 2022). While PFOA and PFOS have not been studied for their carcinogenic potential in humanized PPARa mice. There is sufficient evidence with other ligands to show that hepatocellular carcinogenesis (HC) is unlikely to be induced in a human relevant manner. HC induced by a modestly potent and efficacious PPARa ligands (WY and bezafibrate) is completely absent in the humanized PPARa mouse (Cheung et al., 2004; Hays et al., 2005; Morimura et al., 2006). HC induced by a highly potent/efficacious PPARa ligand (GW7647) is diminished in the humanized PPARa mouse and likely occurs via a different mechanism than in the mice expression mouse PPARa (Foreman et al., 2021a) Perinatal exposure to a high affinity PPARa in humanized PPARa mouse does not result in enhanced hepatocellular carcinogenesis (Foreman et al., 2021b)."

Response 31: Based on analysis of the available data, OEHHA has concluded that not all effects of PFOA and PFOS are mediated solely by PPARα. Detailed analysis of the involvement of PPARα in PFOA and PFOS carcinogenesis is provided in Section 5.7.3 of the draft PHG document. As also discussed in this section, recent animal studies suggest that peroxisome proliferators may induce some liver carcinogenesis in mice via PPARα-independent mechanisms. Thus, the sole involvement of PPARα in PFOA and PFOS-dependent liver toxicity and carcinogenesis is a nuanced issue, and many studies reported on different aspects of possible underlying mechanisms. Detailed analysis of all data (Section 5.7.3) led OEHHA to conclude that PFOA and PFOS-dependent animal carcinogenesis is relevant to human health (also, see the response to Comment 33 from this reviewer).

Comment 32: "Other mechanisms of action [for carcinogenicity] are most certainly at play for PFOA and PFOS (see liver toxicity and dyslipidemia discussions). Activation of CAR, which also is an MIE of PFOA and PFOS, can lead to carcinogenesis. But, again this appears to be specific to rodent CAR (Yamada et al., 2021)."

Response 32: OEHHA concludes that multiple MOAs appear to be involved in PFOA and PFOS carcinogenesis (see the response to Comment 33 from this reviewer). OEHHA did not suggest that activation of CAR was a molecular initiation event (MIE) in PFOA and PFOS carcinogenesis. In fact, OEHHA did not assign a unique adverse outcome pathway (AOP) to PFOA/PFOS carcinogenesis. CAR activation may be one of many MOAs for PFOA/PFOS carcinogenesis in rodents, but its role and relevance in human cancer is unclear.

Comment 33: "Overall, the human data support kidney and testis as targets for PFOA/PFOS-induced carcinogenesis. Although I have found little evidence for biological effects on kidney in rodent models. Most data on liver carcinogenesis in animals should not be considered because this effect is dependent up rodent PPARα and is not a function human PPARα. With that said, evidence from humanized PPARa and CAR models should be taken into account (although little of data has been generated in these models). The increase in pancreatic carcinogenesis in animals is a concern, but it is unclear if this also is dependent upon the presence of mouse, rather than human, PPARa."

Response 33: Section 5.7.3 provides detailed discussion of the relevance of PFOA/PFOS-induced carcinogenesis in animals to human health and of the importance of PPARα in the underlying mechanism. Based on these analyses, OEHHA determined that the cancer data derived from animal studies are relevant to human health. This specifically includes hepatic and pancreatic acinar tumors for PFOA, and hepatic and pancreatic islet tumors for PFOS. The draft PHG cites studies where PPARα knock-out mice exposed to peroxisome proliferators (PFOA and DEHP) still developed liver tumors (Ito et al., 2007; Filgo et al., 2015). This suggests that additional MOAs for liver carcinogenesis in rodents. Furthermore, PPARα activation alone is not sufficient to induce liver tumors in mice (Yang et al., 2007). As such, the MOAs underlying PFOA-induced liver tumors are unclear, so the human relevance of the animal data cannot be dismissed. Additional data with humanized PPARα could help inform interspecies differences in the downstream effects of PPARα activation.

Regarding pancreatic tumors in rats, there is much uncertainty as to whether PPARα activation is solely responsible. PFOA induced pancreatic tumors in rats, whereas the model PPARα agonist Wy-14,643 did not (Biegel et al., 2001), indicating that PPARα activation was not the sole event underlying tumorigenesis in the pancreas. Additional data are needed to elucidate the MOAs linking PFOA exposure to pancreatic tumor formation.

Comment 34: Regarding reduction in weight gain (Section 5.8, *Other Toxic Effects*), "This is a logical endpoint, given that PFOA has been shown to increase energy consumption (shown by indirect calorimetry) (Zheng et al., 2017). However, the analysis does not include what serum concentrations of PFOA and PFOS are associated with reduced weight gain. Also, sex as a variable was not discussed, which can influence this endpoint. Thus, it is difficult to know if reduced weight gain is a sensitive endpoint."

Response 34: The studies listed as reporting PFOA-dependent decreases in weight gain in Section 5.8.1 did not report serum PFOA concentrations. In response to this comment, information for the lowest LOAEL among these studies, i.e., 1 mg/kg-day in Hui et al. (2017) was added.

Comment 35: Regarding adipose effects in section 5.8, "It is not surprising that chemicals that activate PPARa have an effect on adipose, as PPARa activation plays an important role in determining the white vs brite adipocyte phenotype (Chen and

Chao, 2017). However, the studies analyzed do not take into account the fact that mouse PPARa is more efficiently activated by PFOA than human PPARa. Again, whether a human-relevant serum PFAS concentration leads to these effects is not discussed."

Response 35: In response to this comment, the description of PFOA effects on adipocytes in Section 5.8.2 was revised to indicate the possibility of a PPARγ-dependent mechanism. Comparison with Chen and Chao (2017) may not be directly comparable since this study investigated the effects of clofibrate, a typical PPARα and PPARγ ligand, and not PFOA, on adipocyte differentiation. As discussed in the PHG draft document, not all adverse effects of PFOA are PPAR-dependent.

Studies presented in Section 5.8 (*Other Toxic Effects*) are of minor importance relative to the much more robust literature for effects such as liver toxicity and lipid dysregulation for PHG development, which is the focus of the draft document. Discussing the human relevance of every reported adverse effect of PFOA and PFOS in animals is not feasible and was only done for candidate critical endpoints.

Comment 36: Regarding reduced bone quality in Section 5.8, "This is an important adverse endpoint, shown by both human epidemiology and a growing number of animal studies. Please see my comments in the "Developmental and Reproductive Toxicity" section."

Response 36: Please see the response to this reviewer's Comment 26.

Comment 37: Regarding increased blood glucose in Section 5.8, "A number of very recent epidemiological studies (2019-present) supporting an association between aspects of glucose homeostasis and PFOA/PFOS/PFAS body burden have been published. PFOA-related increases in blood glucose in animal models appear to be more consistent than those reported for PFOS."

Response 37: While some recent epidemiologic studies have reported associations between PFAS and markers of glucose homeostasis, other studies have either not identified similar associations or have reported mixed results (Alderete et al., 2019; Charles et al., 2020; Chen et al., 2019; Chen et al., 2020; Christensen et al., 2019; Duan et al., 2020; Fassler et al., 2019; Gardener et al., 2021; Girardi and Merler, 2019; Han et al., 2021; Li et al., 2020; Li et al., 2021; Lin et al., 2020; Mitro et al., 2020; Preston et al., 2020; Rahman et al., 2019; Ren et al., 2020; Valvi et al., 2021; Xu et al., 2020; Ye et al., 2021; Yu et al., 2021; Yu et al., 2021; Zare Jeddi et al., 2021; Zare Jeddi et al., 2021; Zeeshan et al., 2021; Zhang et al., 2022). It should be noted that a number of high quality studies published prior to 2019 did not identify associations between PFOA or PFOS and these same outcomes (ATSDR, 2021). Three recent relevant meta-analyses on this topic have reported mixed results. In one, summary odds ratios for metabolic syndrome were near 1.0 for both PFOA and PFOS (Zare Jeddi et al., 2021). In another, an elevated summary odds ratio for gestational diabetes was reported for PFOA (summary odds ratio = 1.27; 95% CI, 1.02–1.59, n = 8 studies) but

not for PFOS (summary odds ratio = 0.97; 95% CI, 0.86-1.09, n = 8 studies) (Wang et al., 2022). In the third, summary odds ratios for gestational diabetes were near 1.0 for both PFOA and PFOS (Gao et al., 2021).

Potential weaknesses in many of the studies reporting associations between PFOS or PFOA and markers of glucose homeostasis include potential confounding by altered kidney function, potential confounding by correlated PFAS, multiple comparisons issues, small sample sizes, and lack of quantitative dose-response data. Overall, these weaknesses as well as the inconsistency across study results, make it difficult to make firm conclusions regarding the causal or dose-response relationship between PFOA or PFOS and glucose homeostasis at this time.

Comment 38: Regarding mechanistic evidence in Section 5.8, “For the most part, what is presented as potential mechanisms of action are downstream of the molecular initiating event (MIE). What needs to be identified is/are the MIE(s) that occur at the lowest exposure levels (lowest concentrations in in vitro assays). These are most likely going to be activation of nuclear receptors (as discussed above), which are ‘designed’ to respond specifically to very low concentrations of ligands. There is ample evidence that perfluorocarboxcylic acids such as PFOA are ligands for human PPARa and that perfluorosulfonic acids such as PFOS are at best, partial ligands, for human PPARa (e.g., shown and reviewed in Nielsen et al. (2022)). There is growing evidence that PFAS are ligands for PPARa, as well. These two nuclear receptors play important roles in regulating metabolic, adipose and bone homeostasis, thus it is logical that weight gain, adipose phenotype and glucose homeostasis can be altered by PFAS. Given species differences in PPARa in particular, the ability of PFAS to induce adverse health effects via human PPARa need to be demonstrated. With that said, again there is ample evidence of other nuclear receptors (CAR, PXR and PPARg) being activated by PFAS. CAR and PXR also play important roles in metabolic homeostasis (Gao et al., 2009; Spruiell et al., 2014).

The ToxCast database (accessible via the CompTox website) is an important resource for in vitro data on the biological activities of PFOA and PFOS. Care needs to be taken when determining the biological relevance of certain assays within the database. For instance, many of the reporter assays used to describe chemical interactions with nuclear receptors are Gal4 systems in which only the ligand binding domain of the receptor is present in the reporter system. While this can be useful in identifying a ligand for a nuclear receptor, it does not necessarily translate to biological activity given that the response element is not a nuclear receptor response element and that RXR is not required for DNA binding. The most relevant assays are those which use native, human receptors (discussed in Nielsen et al. (2022)). With that said, there are number of analyses with PFOA and PFOS in HepaRG cells, in which the endpoint measured is endogenous gene expression. These support the activation of human PPARa, PPARg, CAR and PXR by PFOA and PFOS and demonstrate differences in potency and efficacy with which they activate these receptors.”

Response 38: OEHHA acknowledges the comment. The ToxCast data for PFOA and PFOS are already presented in Appendix 9 of the draft document. These data are discussed in the *ToxCast High-Throughput Toxicity Screening* subsection of Section 5.8.2.

Comment 39: Regarding Section 6.1, "My only comment with regard to the analysis of human data is that there may be a missed opportunity to consider bone quality as a sensitive outcome of PFAS exposure."

Response 39: Please see OEHHA's response to this reviewer's Comment 26.

Comment 40: Regarding animal data in Section 6.1, "PFOA: Yan et al. (2014) (PMID: 24459700) is not included as a candidate critical study. I think this is an oversight. It is a 28 day study, similar to those listed, with LOAEL = 0.31 mg/kg/day and a NOAEL = 0.08 mg/kg/day based on multiple liver and serum endpoints. There is no comparison to the data supporting the candidate RfD, which is based on reduced ossification during development and a LOAEL of 1 mg/kg/day with a 16 day exposure (Lau et al., 2006). Both of these studies also report serum PFOA concentrations."

Response 40: In response to this comment, the language regarding animal studies in *Dose-Response Assessment* (Section 6.1) has been revised to avoid the impression that a candidate noncancer animal study has been selected. While sensitive studies were analyzed, and their PODs calculated, ADDs were not calculated based on animal data for either PFOA or PFOS due to the availability of human data for the derivation of health-protective concentrations. Because no actual animal critical studies for noncancer endpoints were determined, a detailed analysis of pre-2016 database was not included and was not deemed necessary. To support this conclusion, OEHHA also compared animal and human PODs, finding that human PODs were lower. This clarification has now been added.

Comment 41: In Section 6.1, "PFOS: Guruge et al. (2009) (LOAEL: 0.005 mg/kg/day) should also be considered for the immunotoxicity endpoint. A recent study showed that a 28 day PFOS exposure to 0.0015 mg/kg/day modified distributions of immune cell types while causing a less severe effect on influenza a-induced death (Torres et al., 2021), suggesting a closer estimate of the PFOS LOAEL. Overall, immunotoxic endpoints appear to be more sensitive endpoints that gross changes in liver weight or thyroid toxicity. They also suggest that the POD determined from Dong et al. (2009) is too high."

Response 41: In response to this comment, the PHG draft language regarding animal studies has been corrected to indicate that "recent sensitive animal studies" have been considered in comparison to available human studies, as well as for POD comparisons. Because the health-protective concentration calculations are based on human studies, no formal candidate critical animal studies were identified and a detailed review of the pre-2016 animal toxicity database was not necessary. In any case, it appears that the POD of 16.4 ng/ml from Dong et al. (2009) is much lower than 189 ng/ml, which is the

plasma concentration corresponding to 0.005 mg/kg-day dose group in Guruge et al. (2009). This is more than an order of magnitude difference. While Torres et al. (2021) did not report serum concentrations, they refer to serum concentrations and doses used in Guruge et al. (2009) as being "in a similar range to what was used in this study," and therefore, the former study does not appear to be overall more sensitive than Guruge et al. (2009). Thus, the chosen noncancer POD for PFOS based on Dong et al. (2009) does not appear to be too high.

Comment 42: "PFOA: I concur with justification of the values for RSC and DWI used in the equation. I cannot comment on the choice of the ADD, as I did not review the human data analysis for Chapter 6 given a COI."

Response 42: OEHHA acknowledges the comment.

Comment 43: In Chapter 8, "The analysis found that drinking water concentrations that would be protective of PFOA- (0.007 ppt) and PFOS- (1 ppt) induced cancer were lower than non-cancer endpoints, and thus would be protective for both. My only caution is that PFOA-induced bone toxicity and PFOS-induced immunotoxicity may not have been sufficiently considered and could lower the non-cancer-endpoint-based protective concentration."

Response 43: As described in the response to this reviewer's Comment 26, evidence for bone toxicity of PFOA and PFOS in humans is less robust than for other effects chosen as candidate critical endpoints. Specifically, in the absence of confounder analysis, it is impossible to develop a reliable dose-response analysis for this dataset, thus, no health-protective concentration was derived on this basis.

DR. ROBYN TANGUAY

Comment 1: "An important aspect of the scientific basis of the proposed public health goals for perfluorooctanoic acid and perfluorooctane sulfonic acid in drinking water is the rigorous systematic literature review of the toxicity of PFOA and PFOS in humans and animals models. The review for this assessment report was inclusive of peer-reviewed journal articles, books, reports, and other potentially relevant sources. Since recent systematic reviews were available from the US EPA, New Jersey Drinking Water Quality Institute, and ATSDR (2016-2018 reports) the Office of Environmental Health Hazard Assessment (OEHHA) added searched for additional information available from January 2016 to September 2019. Overall, the literature review is considered systematic and thorough."

Response 1: OEHHA acknowledges the comment.

Comment 2: "Although there is some uncertainty in calculating lifetime average drinking water intake rates, the OEHHA used the most up to date water intake estimates based on US EPA, NHANES, and OEHHA studies. For the health protective goals calculations, the 0.053 L/kg-day is considered appropriate and protective for infants due to their greater exposure to drinking water contaminants."

Response 2: OEHHA acknowledges the comment.

Comment 3: "A critical factor is establishing a drinking water health protection goal is to clearly understand the proposition of chemical exposure in the drinking water relative to other sources of chemical exposure. Numerous studies indicate that the major exposure to PFAS compounds is through contaminated food, and drinking water under most situations will contribute a relatively minor and variable fraction of PFOS and PFOA exposures depending on lifestyle and water consumption sources. The OEHHA recognized this challenge and concluded that it is currently not possible to accurately estimate relevant sources of PFOA or PFOS exposure for California residents, and used a default of 20% for both chemicals. In my view, this is a conservative, but reasonable estimate for the public health goal calculations."

Response 3: OEHHA acknowledges the comment.

Comment 4: "PFOA and PFOS are efficiently absorbed following oral administration in human and animal studies. For all reviewed animal studies oral efficiency exceeded 90% and approached 100% for some doses. There are limited PFOA and PFOS absorption studies in humans, but exposure modeling predicts a somewhat lower absorption rate for PFOA."

Response 4: The draft PHG analyzed exposure modeling and concluded that in most models, uncertainty of consumed dose/absorption efficiency versus uncertainty regarding kinetic parameters such as volume of distribution (V_d) was never satisfactorily resolved. Most modeled studies appear to underestimate PFOA V_d and possibly,

relatedly underpredict PFOA exposure and/or absorption. In the absence of clarity, the assumption of high absorption efficiency is more conservative and health-protective.

Comment 5: "There are well established differences in the bioaccumulation of both PFOA and PFOS between humans and animal models. Measured serum half-lives in animal models range between weeks and months, and is estimated at 2.3 years for PFOA and 5.4 years for PFOS in humans. With these differences, it is most appropriate that OEHHA used human half-life data to reduce uncertainty for calculation of the human protection goal values.

PFOA - Regression analysis of available human epidemiological PFOA exposure data from several locations and exposure scenarios, the PFOA clearance rate of 2.8x10-4 L/kg-day was applied to convert serum levels to applied dose. The considered scenarios, assumptions, and approaches were systematically compared and the final recommendation was well justified in the report.

PFOS - OEHHA used newly available human exposure data from a high PFOS exposure in contaminated drinking water that occurred in Ronneby, Sweden to derive the clearance rate of 3.9x10-4 L/kg-day as a conversion of serum levels to applied dose. The considered scenarios, assumptions, and approaches were systematically compared and the final recommendation for PFOS was well justified in the report."

Response 5: OEHHA acknowledges the comment.

Comment 6: "PFOA – This authors quote the National Toxicology Program (NTP) from the 2016 document 'The NTP concludes that PFOA is presumed to be an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOA on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from epidemiological studies that PFOA reduced infectious disease resistance, increased hypersensitivity-related outcomes, and increased autoimmune disease incidence. The evidence indicating that PFOA affects multiple aspects of the immune system supports the overall conclusion that PFOA alters immune function in humans.'

PFOS –The authors quote the NTP 2016 conclusion 'The NTP concludes that PFOS is presumed to be an immune hazard to humans based on a high level of evidence that PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOS on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from studies in experimental animals that PFOS suppresses disease resistance and natural killer (NK) cell activity. The evidence indicating that PFOS suppresses multiple aspects of the immune system supports the overall conclusion that PFOS alters immune function in humans.'

Overall, the OEHHA identified clear evidence from human epidemiologic data and from animal data that that both PFOA and PFOS are strongly associated with decreased antibody response. Some of the other exposure related changes in functional immunological responses were suggestive in the human epidemiological literature, and the animal data further suggest the immune system is susceptible to PFAS exposures. The final recommended public health goal will thus also set protective levels for the immune system."

Response 6: OEHHA acknowledges the comment.

Comment 7: "PFOA – A careful review of the epidemiologic literature, indicates that PFOA exposures are associated with human hepatotoxicity. The most consistent endpoint is increases in levels of liver enzyme. There are somewhat inconsistent associations between adult PFOA exposures and total cholesterol or low density lipoproteins. There is strong concordant liver toxicity from rat and murine studies. Rodent data consistently identified increased liver weight, histopathological responses, and increased serum enzymes indicative of liver damage.

PFOS – The human epidemiological data for PFOS exposures are less clear, but PFOS exposure studies in rodents indicate clear hepatotoxicity with effects similar to that of PFOA including increased liver weight, liver enzymes, and histopathology. There are somewhat inconsistent associations between human adult PFOS exposures and total cholesterol or low density lipoproteins."

Response 7: OEHHA acknowledges the comment.

Comment 8: "PFOA - OEHHA did not find consistent effects related to the thyroid in the epidemiologic literature. PFOA associated thyroid effects have been reported in environmentally exposed animals, and controlled laboratory studies find positive associations between PFOA and changes in thyroid gland weights and thyroid hormones.

PFOS OEHHA also did not see consistent associations between PFOS and thyroid hormone levels in humans. It is noteworthy that the US EPA had identified three epidemiologic studies that reported positive associations. Subacute rat NTP studies produced decreases in T3 and T4 were observed in both sexes and these effects were observed only in high plasma concentrations. Decreased thyroid weight was reported only in males."

Response 8: OEHHA acknowledges the comment. While some studies of PFOS and thyroid hormone levels identified positive associations, several others did not or they identified associations in the opposite direction (please see Table A7.12 in the PHG document).

Comment 9: "PFOA – A summary of the human epidemiological literature looking for an association between prenatal PFOA exposure and lower birth weight revealed

inconsistent results with no clear trends. Although a few small studies found positive association between PFOA and low birth weight, the majority of studies found no statistically significant associations between PFOA and birth weight. In my view this analysis was compressive and I concur with the authors that there is no clear relationship between prenatal PFOA exposures and decreased birth weight.

PFOS - Although a few studies reported prenatal PFOS exposure related decreases in birth weight, more recent large scale prospective studies failed to report statistically significant associations between prenatal exposure to PFOS and birth weight. In my view the authors were systematic, thorough, and used the most recent data and I agree with the current report conclusion that there is no clear relationship between prenatal PFOS exposures and risk of decreased birth weight."

Response 9: OEHHA acknowledges the comment.

Comment 10: "PFOA – In review of the human epidemiologic literature, OEHHA did not identify consistent evidence that PFOA decreased fertility or fecundity. A large number of animals studies identified reproductive effects in male and female rodents indicating that PFOA is a developmental and reproductive toxicant.

PFOS – A review of the PFOS human exposure data also did not find clear epidemiologic evidence that PFOS exposure decreased fertility or fecundity. However, the recent animal data is consistent with previous findings that PFOS adversely affects reproduction and development systems in rodents."

Response 10: OEHHA acknowledges the comment.

Comment 11: "PFOA- OEHHA comprehensively collected and summarized the recent animal developmental and reproductive toxicity studies. There is strong evidence that PFOA produces adverse developmental and reproductive outcomes in pups. The study by Esterik et al. (2016) is noteworthy as the two highest doses decreased litter sizes and several developmental effects were reported in male and female pups. For example, the OEHHA determined a NOAEL of 0.003 mg/kg-day based on decreased body weight in female pups on PND 4 representing a sensitive PFOA developmental endpoint.

PFOS- OEHHA comprehensively collected and summarized the recent animal developmental and reproductive toxicity studies. There is strong evidence that PFOS produces adverse developmental outcomes in pups. The adverse outcomes were similar to those produced by PFOA, but there is no evidence that PFOS exposures effect litter size."

Response 11: OEHHA acknowledges the comment.

Comment 12: "PFOA – Investigations of the potential neurotoxicity of PFOA are surprisingly limited. Two recent rodent studies (Guo et al. (2019)) reported that high doses decreased brain glutamic acid content and increased glutamate synthetase and

in utero exposure to PFOA (5 mg/kg-day) increased cortical nerve cells numbers in Kunming mouse pups (Qin et al., 2018). I agree with the report authors that more studies are needed to conclusive determine if PFOA is a neurotoxic to animals.

PFOS – The most recent PFOS animal studies are highly suggestive of exposure induced neurotoxicity in vivo and in vitro. There is increasing evidence that PFOS produces neurotoxicity via multiple potential modes of action."

Response 12: OEHHA acknowledges the comment. Neurotoxicity appears to occur following animal exposure to PFOS. Human studies would be useful to investigate the effects of PFOS, if any, on neurotoxicity outcomes suggested by animal data.

Comment 13: "This reviewer is not an expert in cancer risk assessment. Following a thorough review of the human and animal cancer data OEHHA has determined that that PFOA should be evaluated as a carcinogen. The strongest human association is for kidney cancer and thus cross species extrapolations for PFOA is not necessary to calculate the cancer slop factor for PFOA. PFOA also produces liver and pancreatic tumors adding confidence to this determination. Since exposure to PFOA is primarily via ingestion the decision of the OEHHA to calculate a cancer-based health-protective concentration based solely on drinking water consumption is appropriate. The calculated cancer health-protective concentration of 0.007 ppt was selected as the public health guidance using appropriate assumptions."

Response 13: OEHHA acknowledges the comment.

Comment 14: "Following a thorough review of the animal cancer data has determined that determined that PFOS should also be evaluated as carcinogen. PFOS exposures produced liver and pancreatic tumors in male and female rats. Since exposure to PFOS is primarily via ingestion the decision of the OEHHA to calculate a cancer-based health-protective concentration based solely on drinking water consumption is appropriate. The calculated cancer health-protective concentration of 1 ppt was selected as the public health guidance using appropriate assumptions."

Response 14: OEHHA acknowledges the comment.

Comment 15: "A thorough review of the available literature for PFOA indicates that exposures to this chemical is associated with several adverse health effects in humans. Although some of literature of the noncancer endpoints are not congruent, there is reasonable evidence that environmental exposures to PFOA is associated with kidney cancer, reduce immune system and liver functions. Importantly, there is ample experimental animal data that also reports kidney cancer, immunological and liver toxicity. Since human epidemiological studies for PFOA are more sensitive than the animal model data for these endpoints, it is most appropriate to use the currently available human risk of kidney cancer as the endpoint driver. The calculated public health goal for PFOA is drinking water of 0.007 ppt would also be protective for the currently known noncancer endpoints."

Response 15: OEHHA acknowledges the comment.

Comment 16: "A review of the available literature for PFOS indicates that exposures to this chemical is associated with adverse health effects in humans. Although some of literature of the noncancer endpoints are inconsistent, there is evidence that environmental exposures to PFOS is associated with immunological and liver toxicity. The observed elevated total cholesterol association with PFOS in humans is the strongest adverse outcome. Similar to PFOA, the major noncancer effects of PFOS in experimental animals are liver, immune, developmental and reproductive systems. The decision to use the observed increased liver and pancreatic tumor incidence in a two-year rat study to calculate the PFOS public health goal of 1 ppt for PFOS is appropriate with the currently available information. This level should protect against all currently known noncancer toxicities."

Response 16: OEHHA acknowledges the comment.

Comment 17: Concluding Comments: "The OEHHA has adequately reviewed and addressed the available information for both PFOA and PFOS. The methods applied in the derivation of protective health goals based on human kidney cancer for PFOA, and the two-year cancer rat study for PFOS appeared appropriate. In my view the OEHHA adequately addressed all of the important scientific issues relevant for both PFOA and PFOS and the methods applied in the derivation of each health-protective concentration. Although the derived health protective goals for cancer are lower than any of the noncancer endpoints, the proposed noncancer health-protective concentrations were well justified. I am not aware of any missing critical data that that would impact the conclusions made in this report. Finally, based on the available human and animal model data, the recommended public health goals would expect to be protective to vulnerable and sensitive populations."

Response 17: OEHHA acknowledges the comment.

RESPONSES TO COMMENTS MADE DURING THE FIRST PUBLIC COMMENT PERIOD (July 30 – October 28, 2021)

3M COMPANY

Comment 1: "The Proposed PHGs and HPCs are well below any proposed or existing standards and are not based on sound science bases. In fact, the Proposed PHGs and HPCs are so low it is unlikely they could be reliably measured as regulatory standards because they are below method detection limits. As discussed in the detailed technical comments below, OEHHA should revisit the technical bases outlined in the Support Document and bring the Proposed PHGs and HPCs in line with sound science."

Response 1: A PHG is not a regulatory standard. State law requires the State Water Resources Control Board ("Water Board") to consider economic and technologic feasibility in addition to the PHG. Method detection limits may influence the development of the regulatory standards for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). Specific points covered by this summary comment regarding the use of science in the PHG are addressed in Responses to comments below.

Comment 2: 3M suggests that in its analysis of kidney cancer, "OEHHA dismissed other relevant studies that did not demonstrate an association between PFOA and excess kidney cancer cases."

"Based on statements made by OEHHA, both in writing (*see* Support Document at 202, 214 – 216) and verbally during the public webinar, OEHHA appears to have declined to include the Raleigh et al. (2014) study because of the exposure matrix used in that study and misinformation about the data analyses. As discussed in further detail below, 3M respectfully believes OEHHA's criticisms of this study to be misguided." The commenter then included specific details of the Raleigh et al. (2014) study and added, "Unlike the prior mortality studies of this plant, the construction of the exposure matrix for PFOA in the Raleigh et al. study was noted as reasonable by IARC in their Monograph 110 on PFOA (IARC, 2017) where they wrote,

> '*the Working Group noted the reasonable quality of the exposure data. Another strength of this study was the use of incidence data, but this analysis covered only a 20-year period, which limited the number of observed cases for some cancers*.'

Likewise, Steenland and Winquist (2021) also noted the Raleigh et al. study had 'improved exposure assessment with estimation of past cumulative inhalation exposure.' In short, 3M recommends that OEHHA reevaluate its assessment of the cancer risk associated with PFOA to consider additional available data including the Raleigh et al. study. A quantitative assessment for PFOA carcinogenicity based on the epidemiological data considered cannot be supported."

The comment further states, "OEHHA did not provide a detailed analysis of the 'potential reasons' the results from this study [Raleigh et al. (2014)] differ from others regarding the association between kidney cancer and PFOA."

Response 2: OEHHA did not dismiss studies that did not demonstrate an association between PFOA and kidney cancer. All relevant studies were reviewed, and rationale was provided for why a study was included or excluded for dose-response analysis. A thorough discussion of Raleigh et al. (2014) and detailed analyses of the potential reasons why its results differed from those of most other studies is provided in Section 6.2.1 of the PHG document, under *Criteria for causal inference*.

Comment 3: "OEHHA states that Raleigh et al. only had 6 kidney cancer deaths and 16 kidney cancer incident cases with only four in the highest exposure category because of chance and the relatively small numbers of cases in the study. But OEHHA fails to acknowledge that Raleigh et al. is consistent with other studies including the occupational study by Steenland and Woskie (2012), which only had 12 kidney cancer deaths through 2008 and these authors never examined for cancer incidence data. Furthermore, there were no new or additional kidney cancer deaths identified in the study by Steenland and Woskie (2012) because the prior study by Leonard et al. (2008) on the same population had already identified these 12 kidney cancer deaths by the year 2002."

Response 3: Raleigh et al. (2014) is not consistent with Steenland and Woskie (2012) in several very important ways. The latter had twice as many kidney cancer deaths overall and 8-times more in the highest exposure category. In addition, its exposure model was based on serum PFOA concentrations (internal biomarker of exposure) from over 1,300 workers and its results were supported by most other PFOA-kidney cancer studies. In contrast, Raleigh et al. (2014) had fewer kidney cancer deaths, an exposure model of unknown validity, and results that are inconsistent with most other studies.

The fact that the 12 kidney cancer deaths in Steenland and Woskie (2012) were identified in Leonard et al. (2008) does not invalidate the Steenland and Woskie (2012) findings since the former only included a few additional years beyond the latter. It also does not invalidate the other high quality studies that have identified associations between PFOA and kidney cancer (Shearer et al., 2021; Vieira et al., 2013; Barry et al., 2013).

Comment 4: Referring to p. 214 (3rd paragraph) of the draft PHG document, "Comparing the highest exposure category in the Raleigh et al. study (4 kidney cancer cases, Hazard Ratio (HR) = 0.73; 95% CI 0.21 – 2.48) to the highest quartile in Steenland and Woskie study (8 deaths, SMR = 2.66; 95% CI 1.15 – 5.24), OEHHA stated, that in their analyses, the upper quartile in the study by Raleigh et al. is not statistically significant from the SMR estimate reported by Steenland and Woskie. Rather, the OEHHA inferred it being "close (p = 0.08)". OEHHA never showed their data on how this was calculated, but went on to infer that this demonstrates the study could have missed a true association by chance.

OEHHA did not mention that the 2nd highest exposure category in Raleigh et al. study also had 4 additional kidney cancer cases HR= 0.98; 95% CI 0.33 – 2.92). In addition, the OEHHA failed to mention that the 2nd highest exposure category in Steenland and

Woskie study had 0 (zero) kidney cancer deaths (SMR = 0.0; 95% CI 0.0 – 1.48). Combining the upper two exposure categories, Raleigh et al. reported an HR for kidney cancer of 0.85 (95% CI 0.36 – 2.06). Steenland and Woskie did not report the combined upper two quartiles of exposure for an SMR but it can be readily calculated from Table 1 of the Steenland and Woskie study.

SMR = Observed / Expected, meant that there was a total of 9.4 expected deaths for all quartiles combined. These calculations can then be made for the 1st, 2nd, and 4th quartiles which resulted in approximately 0.9, 2.2, and 3.0 expected deaths. This then yields 3.3 expected deaths occurring in the 3rd quartile (compared to the 0 observed deaths). Therefore, combining the upper two quartiles in Steenland and Woskie, there were then 8 observed kidney cancer deaths and approximately 6.3 expected deaths (SMR = 1.27; 95% CI 0.39 – 1.76) for estimated cumulative exposure of PFOA >= 1500 ng/mL-years. Thus, there appears to be no substantial differences between estimates of the magnitude of risk between the upper two exposure categories (albeit different measurements of exposure) in Raleigh et al. study for kidney cancer incidence and Steenland and Woskie study for kidney cancer mortality. As a result, chance is an unlikely explanation for why no association was found.

A reasonable question for OEHHA to have asked is why were there no observed kidney cancer deaths in the second highest exposure category in Steenland and Woskie? Was it chance or could there have been some degree of exposure misclassification? Given the fact there were 8 kidney cancer deaths in this 4th quartile, three of these deaths would have had to been misclassified from the 3rd quartile to make the SMR estimate for the 4th quartile not statistically significant."

Response 4: In response to this comment, reference for the method used (Altman and Bland, 2003) to compare the Steenland and Woskie (2012) and Raleigh et al. (2014) results is now provided in the PHG document.

There are a number of important concerns with the standardized mortality ratio (SMR) presented in the comment above. For one, unlike the SMRs presented in Steenland and Woskie (2012), the SMR presented above has not been peer reviewed. A second concern is that this SMR appears to have been calculated *post priori. Post priori* calculations like this can increase the risk of false positive or false negative results and raise concerns about unwarranted or unjustified data manipulation. Third, studying higher exposures has a number of important advantages, and these may have been diminished or negated by the calculations above. In other words, if true associations exist, higher exposures are usually associated with higher relative risks, and all else being equal, higher relative risks have greater statistical power and are less likely to be impacted by important bias and confounding (Hill, 1965). By combining higher and lower exposure groups, the calculations presented above may have reduced these important advantages. Overall, no rational explanation for combining the upper two exposure groups is provided in this comment. Because of this, and because these calculations have not been peer reviewed, the SMRs presented in the comment above would

receive much less weight in causal inference evaluations than the SMRs already presented by Steenland and Woskie (2012).

The reason why there were no cases in the second highest exposure category of Steenland and Woskie (2012) is unknown, but the wide confidence interval and the small number of kidney cancer deaths in the study overall suggests that this could be due to chance. A note on this issue has now been added to the PHG document (Section 6.2.1, under *Criteria for causal inference*). Importantly, the fact that the third quartile contains no cases does not negate the fact that a very high SMR was identified in the highest exposure quartile of this study or the fact that PFOA-kidney cancer associations were seen in other high quality studies (Shearer et al., 2021; Vieira et al., 2013; Barry et al., 2013).

No supportive evidence or reason is presented in this comment for why three kidney cancer deaths in the highest exposure category of Steenland and Woskie (2012) would be misclassified. OEHHA has found no supporting evidence for this.

Comment 5: Referring to p. 214 (4th paragraph) of the draft PHG document, "The next possible explanation OEHHA puts forward on why the Raleigh et al. study did not find an association between PFOA and kidney cancer was that it did not present any data on confounding variables such as smoking, BMI, or any other known risk factors for kidney cancer except age and sex. The Raleigh et al. study was both an occupational cohort mortality and a cancer incidence study, and as such, detailed information about these variables is not routinely available, especially for the former study design. OEHHA fails to mention that Steenland and Woskie also did not have smoking or BMI, data or any other known risk factors for kidney cancer except age and sex data in their cohort mortality study. Likewise, Vieira et al. (2013) or Barry et al. (2013), did not adjust for BMI in their studies. As for smoking data, Shearer et al. (2021), Vieira et al. (2013), and Barry et al. (2013) adjusted for the categories of smoking (current, past, unknown, or never) with only Barry et al. (2013) adjusting for the much more quantifiable, time-varying measurement of smoking data. And OEHHA chose not to consider the Barry et al. results."

Response 5: That other mortality studies may or may not have data on potential confounders, or that these data are "not routinely available" in some study types, has no bearing on the fact that Raleigh et al. (2014) did not have this information or that this is a weakness of this study. The commenter is correct that Steenland and Woskie (2012) did not have data on smoking and body mass index (BMI). However, despite not having these data, the Steenland and Woskie (2012) results were reasonably consistent with the other high quality PFOA-kidney cancer studies, while the Raleigh et al. (2014) results were not. Finally, confounding is a particularly worrisome concern in Raleigh et al. (2014) given the major differences in all-cause SMRs reported between the exposed and unexposed groups.

It was noted in the draft PHG document that Vieira et al. (2013) did not have data on BMI, and that there is no evidence that BMI caused major confounding in this study.

This lack of evidence for confounding by BMI also applies to Barry et al. (2013), which took place in the same study area as Vieira et al. (2013).

The idea that the elevated odds ratios in Shearer et al. (2021) and Vieira et al. (2013) would go away (i.e., be close to 1.0) with a more refined adjustment for smoking is implausible. Even if every person with high PFOA exposure smoked, and every person with low PFOA exposure did not smoke (an extreme and farfetched scenario), a more refined adjustment for smoking could not change a kidney cancer odds ratio near 2.0 to an odds ratio near 1.0. This can be easily seen using the methods and calculations for evaluating confounding presented by Axelson (1978).

OEHHA did consider the Barry et al. (2013) results. This study and its results are discussed and referenced throughout the document, and it played a very important role in supporting the findings of the two studies (Shearer et al., 2021; Vieira et al., 2013) that were used to calculate the PFOA PHG. OEHHA could not select both Barry et al. (2013) and Vieira et al. (2013) for its PHG calculations since these studies likely involved overlapping participants and using both would result in an inappropriate overweighting of these subjects. This was noted in the PHG document as well. It was further noted that Vieira et al. (2013) was selected over Barry et al. (2013) because it provided information on dose-response that was more useful.

Comment 6: Referring to p. 214 (4th paragraph) of the draft PHG document, "The Support Document also states that "the higher SMRs seen in the St. Paul workers for outcomes not known to be associated with PFOA show that these workers were generally less healthy than the Cottage Grove workers and provide evidence that the St. Paul Plant workers were not an appropriate comparison group." SMR analyses were provided for both the 3M Cottage Grove plant and the 3M St. Paul plant. Both plants had SMRs calculated with the Minnesota mortality rates for comparison purposes. Importantly, the SMRs from each of these two cohorts used different standards meaning these SMRs are not directly comparable to one another as readily seen in Table 1 of Raleigh et al. There was a 9-year mean year of birth difference between the two cohorts. The SMRs are not directly comparable without further adjustment. When researchers cannot be confident that the bias due to comparing SMRs directly is small, estimates should be based on a single common standard applied such as those used in a regression model that accounts for the differences among the compared populations and the effects of exposure on person-time (Rothman et al., 2008).

Therefore, to compare the PFOA-exposed population with the non-exposed population, Raleigh et al. estimated hazard ratios (HR) with 95% CIs for mortality and cancer incidence as a function of PFOA time-dependent exposure using extended Cox regression models. Raleigh et al. stated,

> '*To compare the APFO-exposed population with the nonexposed population, HR with 95% CIs for mortality and cancer incidence risk were estimated as a function of APFO time dependent exposure using extended Cox regression models. In these models, the Saint Paul workers were the referent population and APFO*

> *exposure in the Cottage Grove population was classified into quartiles. The time scale was age, beginning at the date of first employment for the mortality analysis and the later of date of first employment or 1 January 1988 (when registry data were available) for cancer incidence. Follow-up continued until death, diagnosis of the cancer of interest or end of follow-up. Models were adjusted for year of birth and sex*.'

OEHHA's statement that "the higher SMRs seen in the St. Paul workers for outcomes not known to be associated with PFOA showed that these workers were generally less healthy than the Cottage Grove workers provides evidence that the St. Paul workers were not an appropriate comparison groups" suggests that OEHHA is inappropriately comparing the SMRs directly when age and/or sex distributions differ without a common standardization and/or regression analyses. The St. Paul plant was an appropriate referent when analyzed by Cox proportionate hazard models. Raleigh et al. (2014) also stated the results did not change appreciably when the PFOA exposures were lagged by 10 years.

Response 6: Both the Cottage Grove and St. Paul SMRs use Minnesota state rates as the "unexposed" comparison group, and both sets of SMRs are standardized by sex and age. While it is true that the average ages at follow-up differed between exposed Cottage Grove and unexposed St. Paul workers (63.2 vs. 68.8 years, respectively), the commenter does not provide an explanation for why this difference would cause such a large difference in all-cause or all-cancer SMRs. In other words, the implication appears to be that once the Cottage Grove workers age another five years, their all-cause ***age-adjusted*** SMR is likely to increase to a level that is close to St. Paul. This would be an increase of >15% (i.e., from 0.85 to 0.98). However, no evidence or rational explanation for why this is likely to occur is presented.

OEHHA agrees that the Cox regression models should help account for differences in cumulative PFOA exposure, sex, and age. However, it would not account for any other underlying differences in health, health-related behaviors or other risk factors between the Cottage Grove and St. Paul workers. As such, this model by itself would not account for the possibility that the St. Paul workers are not an appropriate control group for this study.

Comment 7: Referring to p. 214 (5th paragraph continuing onto p.215) of the draft PHG document, "OEHHA was also critical of the Raleigh et al. study because ground water contamination had been "well-documented" near the Cottage Grove facility but no information was available on non-work related residential exposures. Exposures from drinking water were considered small relative to the occupational exposures for the Raleigh cohort. Indeed, in Woskie et al. (2012), the authors likewise stated the following in their development of their exposure matrix for the Steenland and Woskie cohort mortality study:

> '*Another influence on worker serum levels may have come from personal exposures via water in communities surrounding the plant (Emmett et al., 2006;*

> *Steenland et al., 2009a). The exposure estimates reported here do not explicitly account for residential exposures over time, although it is believed that relative to workplace exposures these are relatively small. For example, current workers were reported to have a median serum PFOA level of 0.147 versus 0.074 ppm for former workers and 0.027 ppm for current/former residents in the study of the nearby community member PFOA levels (Steenland et al., 2009b).*'

Potential residential exposure therefore does not provide grounds for dismissing the study."

Response 7: The serum PFOA levels provided above are for the C8 study area and not for the Cottage Grove area. As such, their relevancy to Raleigh et al. (2014) is unknown. It should also be noted that Raleigh et al. (2014) was not dismissed, and that OEHHA spent considerable time and effort evaluating this study (please see Section 6.2.1 of the PHG document, under *Criteria for causal inference*).

Comment 8: Referring to p. 215 (1st paragraph) of the draft PHG document, "OEHHA provided only a very brief description taken from the Raleigh et al. (2014) published paper as to the process used for the construction of the exposure matrix. We refer OEHHA to Chapter 4 of the study's publicly available dissertation. See Exhibit A."

Exhibit A can be found in the publicly available 3M comments.[1]

Response 8: In response to this comment, a description of the exposure matrix used by Raleigh et al. (2014) is now provided (Section 6.2.1, under *Criteria for causal inference*). It should be noted that Raleigh et al. (2014) provides only a limited description of their exposure assessment methods, and several key details, e.g., critical high quality exposure validation data, are missing. This lack of information is an important weakness of the study. The Raleigh thesis cited by the commenter may include some more relevant information, but the quality of this thesis and the extent with which it has been peer-reviewed are unknown. As described in the *General Methods* section of Appendix 7, OEHHA relied on published studies for this assessment, and the Raleigh thesis would not meet this criterion for inclusion.

Comment 9: Referring to p. 215 (2nd paragraph) of the draft PHG document, "OEHHA suggests that little to no information is available on the degree to which inhaled PFOA is absorbed in humans or the inter-individual factors that might affect his absorption. While there have not been inhalation studies of PFOA in humans, in their review paper, Griffith and Long (1980) and Kennedy Jr et al. (1986) unquestionably concluded that PFOA is efficiently absorbed in laboratory animals following inhalation exposure and that it is not metabolized and is eliminated intact (as reviewed by Kennedy et al. (2004)). The findings from Griffith and Long (1980) and Kennedy Jr et al. (1986) demonstrate that

[1] https://oehha.ca.gov/media/dockets/20426/20531-3m/2021-10-28_final_3m_comments_on_public_review_draft_oehha_phg_technical_support_document.pdf, accessed on 4/23/2022

effective serum uptake of PFOA has been shown under both acute and repeated inhalation exposures in rats."

3M then presents a description of the results from Griffith and Long (1980) and Kennedy Jr. et al. (1986).

Response 9: The commenter addresses the key issue here: there are no relevant studies in humans. However, other major toxicokinetic differences between humans and rats have been documented for PFOA, and these known differences highlight the considerable uncertainty associated with extrapolating toxicokinetic data from rats to humans.

Comment 10: Referring to p. 215 (2nd paragraph) of the draft PHG document, "OEHHA also criticized the method of exposure assessment in Raleigh because "the PFOA exposure estimates … were not based on actual PFOA measurements." While no specific biomonitoring validation data were presented, there is strong collaborative evidence that the jobs and tasks with the highest air exposure monitoring data in Raleigh et al. study were, indeed, consistent with the higher PFOA serum concentrations measured. This can be inferred from reading Raleigh et al. (2013, 2014), Olsen et al. (2000), and Olsen et al. (2003).

A review of the 3M Cottage Grove plant operations provides this perspective. APFO production began at the 3M Cottage Grove plant in 1947. APFO was produced via a five-stage process: electrochemical fluorination; isolating and converting the chemical to a salt slurry; converting the slurry to a salt cake; drying the cake; and packaging. The greatest likelihood for exposure occurred in the drying area (Olsen et al., 2000; Raleigh et al., 2014). This is substantiated by Raleigh et al. (2013) who provided the range of TWA (mg/m^3) for APFO exposure by specific job titles and years. While Raleigh et al. (2012)[2] reported job titles affiliated with electrochemical fluorination (head cell operator, APFO kettle room operator) that had ranges of APFO TWAs (mg/m^3) up to 0.04 mg/m^3 APFO, those involved with the operation of the spray dryer had measurements that ranged up to 100 fold higher (0.124 mg/m^3). Less exposed job titles including clerk, custodian, and finished good checkers had TWAs much lower (<= 0.002 mg/m^3).

While Olsen et al. (2000) did not report biomonitoring data by job titles, much effort for exposure reduction was made in the drying area where the highest PFOA blood levels were known to exist. Thus, while the median PFOA serum levels reported in 1993, 1995, and 1997 were 1100 – 1300 ng/ml (Olsen et al., 2000), the mean values were 5000 – 6800 ng/ml owing to the subset of workers with much higher concentrations that ranged as high as 11400 ng/mL. These employees were generally recognized as having had exposures in the drying area. The PFOA concentrations that have been reported in the employees at the 3M Cottage Grove plant are in the similar range of concentrations for those reported in the construction of an exposure matrix for the DuPont Washington Works plant by Woskie et al. (2012) who found that, among those

[2] 3M did not provide reference for Raleigh et al. (2012).

working with fine powder production had the highest PFOA serum concentrations (see Table 2)."

Table 2, which can be found in the publicly available 3M comments,[3] presents PFAS serum concentrations for different categories of workers.

"Taken all together, all these data showed compelling evidence that inhalation exposure was highly likely and the job and the task-based exposure matrix used by Raleigh (2012, 2014) was consistent with biomonitoring data historically reported at the 3M Cottage Grove Plant."

Response 10: Quality and validation of exposure data are key aspects of any environmental or occupational epidemiology study, and generally should not be "inferred." With regard to Table 2 in the 3M comment, it should be noted that 91% of the workers in this table are not from the 3M plant. With that in mind, OEHHA agrees that there is some, albeit limited, evidence that the Raleigh et al. (2014) exposure model might be partially accurate in reflecting broad exposure trends. However, without a proper validation study, which has not been done, it is unknown exactly how accurately this model can be used to reflect the true cancer risks of PFOA. Without a proper validation study it is difficult, if not impossible, to assess the likely degree and direction of any bias caused by errors in this model.

Comment 11: Referring to p. 217 (1st paragraph) of the draft PHG document, "In selecting only two studies for their PFOA PHG analysis, OEHHA dismissed other relevant studies that did not demonstrate an association between PFOA and excess kidney cancer cases. … [A]mong three occupational analyses (Barry et al., 2013; Raleigh et al., 2014; Steenland and Woskie, 2012), which likely represent the highest exposed individuals based on overall reported biomonitoring data, only one analysis showed a statistically significant association with kidney cancer. However, that association was not seen when the two highest exposure categories were used. None of these data were considered by OEHHA in their construction of a PHG for kidney cancer. And there remains the confusing possibility of overlapping of kidney cancer cases between Steenland and Woskie (2012), Vieira et al. (2013), and Barry et al. (2013) This was acknowledged by Steenland and Woskie (2012) but they did not provide any insights as to the percentage. And the Shearer et al. (2021) single serum PFOA concentrations measured at general population levels are inconsistent with the other 4 studies. An excess of renal tumors have not been reported in three stocks of Sprague Dawley rats by NTP (2020), Butenhoff et al. (2012a), and Biegel et al. (2001)."

Response 11: It should be noted that basing conclusions solely on statistical significance is frequently a misleading approach (Greenland et al., 2016). With this in mind, it should also be noted that Barry et al. (2013) did report a statistically significant increase in PFOA-related kidney cancer among community members. And, although the

[3] https://oehha.ca.gov/media/dockets/20426/20531-3m/2021-10-28_final_3m_comments_on_public_review_draft_oehha_phg_technical_support_document.pdf, accessed on 4/23/2022

risks were somewhat unclear in workers, the number of workers was much smaller than the number of community members. Another problem with the analyses of workers is that certain key details were not provided. For example, the exposure levels in these workers were not given. It should also be noted that while the hazard ratio (HR) in the highest quartile for workers in Barry et al. (2013) was not elevated, the HR in the 3rd quartile was (HR = 3.27; 95% CI, 0.76-14.10). Although not statistically significant, this HR suggests an over 3-fold increase in risk, and this increase is similar to those seen in other high quality studies of PFOA and kidney cancer (Shearer et al., 2021; Vieira et al., 2013).

The PHG document contains considerable discussion of the Raleigh et al. (2014) and Barry et al. (2013) studies (see Sections 5.7.1 and 6.2.1 and Tables 6.2.5, A7.21-27, and A12.1 in the draft PHG document), so any claim that these studies were "dismissed" is unwarranted.

OEHHA agrees that there was likely some overlap among the participants of the three C8 studies (Vieira et al., 2013; Barry et al., 2013; Steenland and Woskie, 2012), and this is why these studies were not combined in the PHG calculations (see the response to Comment 5 on this issue).

The serum PFOA concentrations in Shearer et al. (2021) are presented and discussed throughout the document (for example see Figure 6.2.3). The fact that these exposures are likely similar to those in the general US population is also noted (Section 6.2.1).

OEHHA agrees that increases in renal tumors have not been seen in PFOA-exposed rats. However, as noted in the PHG document, increases in other cancer types have been seen in laboratory animals exposed to PFOA. It should be noted that site concordance across species is not a requirement for conclusions regarding cancer in humans. A good example of this is arsenic. Arsenic is an established human carcinogen despite the major differences between laboratory animals and humans in the types and risks of cancer that arsenic causes (Vahter, 1999).

Comment 12: "OEHHA should not use serum ALT as a POD due to minimum variance explained in epidemiological studies and the fact that there is no increased risk for liver disease."

"In developing the proposed HPC for PFOA, OEHHA misrepresents the relationship between alanine aminotransferase (ALT) and PFOA and how it relates to 'liver damage' or 'liver function.' ALT is a 'leakage' enzyme and may be increased due to necrosis, injury or repair. Increases of two- to four-fold in rodents, canines, non-human primates, and humans indicate hepatic injury. As defined by Hall et al. (2012):

> '*Based on the recommendations of regulatory authorities, (EMEA 2010; FDA 2009; HED 2002) increases in ALT activity of two-to threefold should be considered as indicated of 'hepatocellular damage*.'

As will be discussed below, several studies in the scientific literature that have suggested an elevation of ALT remain well-within the expected physiologic range of measured ALT and therefore, using the term 'damage' is misleading. It is also possible to have quite modest but statistically significant increases in ALT that are not toxicologically relevant (Cattley and Cullen, 2013). The human half-life of ALT is approximately 47 hours with significant variation of 10 – 30% on a day-to-day basis with circadian variation (Córdoba et al., 1998; Kim et al., 2008). Most cohort studies examining estimated serum PFOA concentrations when there is only a single ALT measurement period fail to note this variation in half-life."

Response 12: The elevations in alanine aminotransferase (ALT) seen in some human studies may be "modest" in some otherwise healthy individuals but they are likely to be quite important on a population basis or in people with pre-existing liver conditions. This is discussed in Section 5.2.5 of the draft PHG document.

The documents referenced by the commenter on "hepatocellular damage" refer to laboratory animals, not humans. This is important because the study OEHHA used to establish its noncancer HPC for PFOA was done in humans (Gallo et al., 2012). Equally important is that this study used a long established and widely accepted clinical guideline to define an elevated ALT level. As discussed in the draft PHG document (Section 6.2.1), ALT levels above this clinical guideline have been linked to major increases in morbidity and mortality in human studies.

OEHHA agrees that some intra-individual variation exists in serum ALT. Importantly though, because ALT levels were assessed using the same methods in all participants, any resulting bias is most likely non-differential and therefore most likely to bias results towards the null, not towards the positive associations identified. This is now noted in the revised draft PHG document (Section 6.1.1).

Comment 13: "From a disease standpoint, nonalcoholic fatty liver disease is the most common cause of mild elevations of liver enzymes (Giannini et al., 2005). Liver function should be considered in the context of many different biological processes that occur within the liver including: 1) production of proteins for plasma; 2) regulating blood clotting; 3) production of cholesterol and lipoproteins; 4) conversion of excess glucose to glycogen for storage; 4) regulation of blood amino acids; 5) metabolism of toxins; 6) production of bile; and 7) clearance of bilirubin."

Collectively, the studies assessed by OEHHA do not suggest 'liver damage' (see above definition of a 2 to 4- fold increase) as measured by ALT associated with increasing serum concentrations of PFOA. As discussed in detail below, none of these studies, except Convertino et al. (2018), measured aspects of liver function that involved measures of blood clotting. Although some studies' regression coefficients for PFOA may be statistically significant, the percent variation of ALT explained by PFOA is often minimal, at best, and the increase of ALT is very modest (generally an increase of 1 to 5 IU ALT). Nor was there evidence of increased mortality from increased liver disease in epidemiologic analyses of a community-based exposure to PFOA from drinking water

(Darrow et al., 2016), or in occupational cohort mortality studies (Raleigh et al., 2014; Steenland and Woskie, 2012). These later two studies are limited by the number of deaths reported.

In conclusion, there is no apparent association between PFOA and liver disease including enlarged liver, fatty liver, or cirrhosis based on epidemiological studies. Small percentage changes in ALT have been reported in some epidemiology studies across quite different perfluoroalkyl concentrations but are within normal physiological ranges. This small magnitude of change of a liver biomarker, if it presents, does not indicate liver damage by any standard clinical practice of medicine. Confounding cannot be ruled out as a possible explanation for this observation due to the many factors that can influence ALT. Thus, there is insufficient evidence of an association between PFOA and ALT in humans, and the calculation of an HPC for PFOA at general population levels by OEHHA on these grounds is unwarranted."

Response 13: OEHHA agrees that the liver is involved in many vital physiologic processes, and this highlights the importance of any chemical exposure that affects the liver. The fact that liver physiology is so complex also highlights the difficulties of examining "liver disease." This is because "liver disease" is not just one disease but a combination of many different diseases. To date, most studies that have examined PFAS and "liver disease" have combined all or most of these individual diseases. In all likelihood, however, not every hepatotoxic chemical causes every different type of liver disease. Because of this, PFOA studies that combine all liver diseases may be including both liver diseases that are caused by PFOA and liver diseases that are not caused by PFOA. This would dilute any real effects PFOA causes and make it difficult to identify the true toxicity of this chemical in these studies.

The notion that the percent variation in ALT explained by PFOA is "minimal" ignores the potentially large or very important impacts these effects may have either on a population basis or in people with pre-existing liver disease. It also ignores the fact that there are many reasons for variations in ALT. The finding that PFOA does not explain all or most of the variation in ALT does not mean that PFOA is not a preventable cause of these variations; it simply means it is not the only cause (which is already known). A good analogy can be seen by looking at the causes of lung cancer. Clearly, smoking is the number one known cause of lung cancer. However, if one were to ignore all other causes of lung cancer, then one would have to ignore the tens of thousands of non-smokers who die of lung cancer each year. Similarly, if one were to ***only*** focus on the number one known cause of liver pathology (which is probably viral hepatitis), then one would have to ignore all the people who develop or die of liver pathology due to any other hepatotoxic cause (like PFOA).

The commenter also notes another major weakness in several of the studies they cite: small sample sizes. Because several of these studies had very few cases of liver disease, they may not have had sufficient statistical power to identify real effects. To date, other than the possible exception of one study of Gilbert Syndrome (Fan et al., 2014), no large scale high quality study of PFOA and any specific liver disease has

been done. This is not surprising because a high quality study like this would require a relatively large number of cases, good long-term exposure data, unbiased subject selection, appropriate information on potential confounders, strict and specific case definitions, and thorough case ascertainment. Given the high complexity and costs of studies like this, it seems unlikely that this type of research will be funded, completed, and published in the foreseeable future (if ever). Importantly though, studies like this may not be needed. ALT is an easy to measure, widely accepted, accurate, sensitive, and clinically relevant biomarker of liver toxicity. And, a number of high quality studies of PFOA and ALT have already been done. As a whole, these studies have shown that PFOA alters ALT and therefore have shown that PFOA disrupts normal liver function.

It should be noted that OEHHA has identified many studies that did report statistically significant associations between PFOA and ALT, and several of these are of very high quality. These studies are described in the draft PHG document.

Comment 14: "The study by Gallo et al. (2012), which was used by the OEHHA to derive the HPC for PFOA, relied on the C8 Health Project cross-sectional data collected in 2005-2006. They found a positive association between PFOA and serum ALT. Based on 3 different regression models, Gallo et al. reported statistically significant ln-PFOA (ng/mL) beta coefficients in models where ln-ALT was the independent variable.

It is important to note, however, that these three models had an increasing number of covariates (2, 7, and 11) besides PFOA in each model. The R^2s of these three models were 0.170, 0.174, and 0.265, respectively. However, the partial R^2 for PFOA (difference between R^2 including and excluding PFOA) remained 0.002, 0.001, and 0.002 for these three models, respectively. This clearly does not suggest that PFOA was a substantive contributor to the increase of ln-ALT because it only explains between 0.1 and 0.2 percent of the variance in ln ALT. The coefficient was only statistically significant because of the study sample size (N = 47,092). OEHHA did mention this very low partial R^2 in the regression modeling that was done by Gallo et al., but relied on the study nonetheless."

Response 14: Please see the response to Comment 13 above. Because a number of different factors can affect serum ALT levels, including normal diurnal variation, normal day-to-day variation, laboratory imprecision, and a number of other factors, it is not expected that PFOA would be associated with large R^2 values. Rather, given the multitude of factors that can influence ALT, relatively small R^2 values are the expectation. Most importantly though, regardless of whether the R^2 values are large or small, Gallo et al. (2012) still found strong evidence that PFOA increases serum ALT, a well-known biomarker of adverse liver effects (Gallo et al., 2012).

The Gallo et al. (2012) findings were statistically significant not only because of the large sample size. They were statistically significant because of the large sample size ***and because PFOA was associated with an increased serum ALT.*** Without the latter, a statistically significant association would not have been seen.

Comment 15: "Based on their fitting values of ALT by deciles of PFOA (given the mean values of the covariates), Gallo et al. showed a mean (untransformed) ALT of approximately 20.9 IU/L at 6 ng/mL PFOA that increased to approximately an ALT of 22.2 IU/L at 30 ng/mL PFOA (+1.3 IU/L increase in ALT) but plateaued thereafter. The highest decile was 23 IU/L ALT associated with approximately 320 ng/ml PFOA. It should be noted that the upper normal reference range (depending on laboratory) for ALT is approximately 45 IU/L."

Response 15: In addition to the results given by the commenter, Gallo et al. (2012) also reported that PFOA increased the odds of having a clinically relevant increase in ALT (Gallo et al., 2012). As already noted in Section 6.1.1 of the draft PHG document, these latter results, and not those cited by the reviewer, are the basis of OEHHA's noncancer HPC for PFOA.

Comment 16: "OEHHA should not rely on the enzyme findings from Gallo et al. (or Darrow et al. discussed below), which suggest 'liver damage' is associated with PFOA. In fact, the C8 Science Panel (2012) admitted the lack of evidence for the association between PFOA and liver disease, stating:

> 'From our studies of patterns of diagnosed liver disease there is no evidence of any increased risk of liver disease in relation to PFOA exposure. Based on our studies of liver enzymes and inconsistent findings in reported literature there is some evidence of small shifts in liver function, mainly within the normal physiologic range, being associated with increasing PFOA exposure. It is uncertain if PFOA is the cause of the association, but if so there is no evidence that this is reflected in any increase in overall incidence of diagnosed liver disease. Therefore, the Science Panel does not find a probable link between exposure to PFOA and liver disease.'

Other studies show there is no apparent association between PFOA and liver disease, including enlarged liver, fatty liver, or cirrhosis based on epidemiological studies."

Response 16: Stating "there is no evidence" of an association is a much different conclusion than stating that there is strong evidence that no association exists. The C8 panel concluded the former, not the latter. This is important because the latter is needed to conclusively state that PFOA does not cause liver disease. A conclusion that PFOA does not cause liver disease requires that adequate research has been done, and this has not been the case. Please see the response to Comment 13 for further discussion of this issue. The commenter did not provide the C8 Science Panel (2012) reference.

Comment 17: "In their cross-sectional analysis, Darrow et al. (2016) suggested the results of the C8 Science Panel's community worker cohort study were consistent with the Gallo et al. (2012) (above) showing an increasing trend in the β coefficients across quintiles. … Darrow et al. (2016) did not provide R^2 or partial R^2 values in these cross-sectional analyses. Neither study adjusted for serum lipids (see below discussion by Deb et al. (2018)).

In their analysis of estimated cumulative exposure of PFOA in the C8 Science Panel's community and worker study on liver function and disease, Darrow et al. (2016) provided the linear regression coefficients for ln-transformed ALT per ln-PFOA (see Table S1 of Darrow et al. (2016)). The R^2 for these 3 models were … similar in magnitude to Gallo et al. for the same models, adjusted for the covariates in their cross-sectional analysis. However, PFOA in Darrow et al. (2016) was an estimated cumulative ng/mL-year metric versus measured (ng/mL), and unlike Gallo et al. (2012), Darrow et al. (2016) did not show the partial R^2 for PFOA.

Because the coefficients of determination for the Darrow et al. models 1, 2, and 3 are very similar to Gallo et al. (despite a different metric for PFOA), it is highly likely the partial R^2 for PFOA in the Darrow et al. study also remained in the extremely low range. Thus ln-PFOA (ng/ml-years) explained very little of the variance of ln-ALT in the Darrow et al. study, as shown in Table S1 of its publication."

Response 17: Without the actual partial R^2 values from Darrow et al. (2016), commenting on what these R^2s would likely be is mostly conjecture . Regardless, please see the response to Comment 14 from this commenter regarding low R^2 values. A conclusion that PFOA is an important and preventable cause of increased ALT is not inconsistent with a low R^2.

With regard to adjusting for serum lipids, please see the response to Comment 19 below.

Comment 18: 3M describes several epidemiological studies and reports (Convertino et al., 2018; Costa et al., 2009; Olsen, 2018; Olsen and Zobel, 2007; Sakr et al., 2007b; Sakr et al., 2007a) they claim did not find significant associations of PFOA and ALT.

Response 18: It should be noted that some of the studies the commenter describes as not finding "significant" associations did report regression coefficients that support the conclusion that PFOA increases ALT. For example, although not statistically significant, Sakr et al. (2007a), Sakr et al. (2007b), and Olsen et al. (2007) all report positive associations between PFOA and serum ALT. In fact, in several of these studies, the effect sizes are similar to those reported in the study OEHHA used to develop its HPC (Gallo et al., 2012), and several are borderline statistically significant (e.g., two sided p-values <0.10). In fact, one could argue that given the known hepatotoxicity of PFOA in laboratory animals, one-sided p-values should have been used and that the more relevant p-values in these studies are actually lower than those reported. Overall, based on a number of different studies, OEHHA has concluded the current literature provides strong evidence that PFOA increases serum ALT.

Comment 19: "Several of the studies reported by OEHHA analyzed NHANES data. The challenges of using NHANES biomonitoring data to incorporate into any form of risk assessments has been well-described by Sobus et al. (2015). In this regard, both Lin et al. (2010) and Gleason et al. (2015) have analyzed multiple 2-year cycle NHANES cross-sectional data with liver enzymes and PFOA or PFOS. As part of their analysis of

NHANES data, Lin et al. or Gleason et al have not been able to address an important methodological limitation regarding the relationship between liver enzyme and serum lipids.

As shown by Deb et al. (2018) in their analysis of NHANES data from 1999-2012, there is an association between measured liver enzymes and lipid levels. Deb et al. reported that LDL was associated with a 2-fold increase in odds of an elevated ALT and AST measurements. Any association between perfluoroalkyls measurements and liver enzymes should consider adjusting for age, sex, race/ethnicity, and lipids. If lipids are associated with liver enzymes, then lipids might be a confounder in studying the association between perfluoroalkyls and liver enzymes.

However, some suggest PFOA may be associated with lipids (at lower PFOA concentrations). Therefore, lipids, at low concentrations, might be on the causal path between the exposure (perfluoroalkyls) and increased liver enzymes. OEHHA offered no insights into the relationship between perfluoroalkyls, lipids, and liver enzymes."

Response 19: Sobus et al. (2015) did not provide any specific recommendations for evaluating PFOA-ALT associations. It should also be noted that the focus of Sobus et al. (2015) was on using data from the National Health and Nutrition Examination Survey (NHANES), and OEHHA did not use NHANES data to calculate its HPCs. With all of this in mind, OEHHA agrees that Sobus et al. (2015) provides some valuable recommendations. However, OEHHA has an extensive history of using and evaluating NHANES data, and was well aware of the practices recommended by Sobus et al. (2015) before its publication.

Regarding serum lipids, if serum lipids are in the causal pathway between PFOA and increased ALT then serum lipids are not a confounder, and as such should generally not be adjusted for in the statistical analyses. And, if lipids are indeed in the causal pathway, then that would mean that PFOA ***causes*** an increased ALT, which is the conclusion reached by OEHHA.

Comment 20: "In addition, in their analyses of 2011 – 2014 NHANES data, Jain and Ducatman (2019) reported there was no association with serum ALT and PFOA in non-obese people. The Canadian Health Measures Survey (Fisher et al., 2013) contains no self-reported cases of liver disease arising from the NHANES data (Melzer et al., 2010). There are also no self-reported cases of medically validated liver disease with exposure to PFOA in the C8 Health Panel study (Darrow et al., 2016), including fatty liver disease.

It is incorrect to infer that the weak associations between ALT and measured perfluoroalkyls, in populations whose serum PFAS concentrations can be orders of magnitude different, cause any increased risk of liver disease. Numerous confounding factors must be considered in analyses of ALT. These include the usual confounders of age, sex, body mass index, alcohol, glucose in women, physical activity, smoking, triglyceride level, total cholesterol, and exposures to toxins in an environmental and/or occupational setting."

Response 20: With regard to the Jain and Ducatman (2019) findings on obesity, this finding has yet to be replicated in another study population. Even if these findings were replicated and considered valid, OEHHA's HPCs are not just aimed at non-obese people; they are aimed at protecting all population groups.

With regard to confounding, no evidence is presented in this comment that any of the factors mentioned caused major confounding. In its extensive evaluations, OEHHA found no evidence for this either. Please see the discussion on confounding in Section 6.1.1 of the draft PHG document.

Comment 21: Referring to p. 141, (2nd paragraph) of the draft PHG document, "We do not disagree with the analysis of liver cancer and PFOA in Eriksen et al. (2009) (e.g., range 5th percentile men for liver cancer was 2.5 ng/mL and 13.7 ng/mL for the 95th percentile). However, the exposure range reported in Shearer et al. (2021) should be discussed as limited in the preceding paragraph on kidney cancer, just as the exposure ranges were limited in the Eriksen et al. (2009) study."

Response 21: The problem with having a somewhat limited range in exposures is that, in general, this can make it more difficult to identify true effects, and it is unlikely to cause a false positive result. As such, this potential source of bias was a greater concern for Eriksen et al. (2009) than for Shearer et al. (2021) because the former found no effect while the latter identified an association (Eriksen et al., 2009; Shearer et al., 2021). Overall, when a potential for bias is being evaluated, both its likely magnitude ***and its likely direction*** should be considered, and this is what OEHHA has done.

Comment 22: Referring to p. 141 (2nd paragraph) of the draft PHG document, "Unlike liver cancer and TFE reported in rodent studies discussed in this paragraph, OEHHA did not mention in the previous paragraph on kidney cancer that TFE caused an increased incidence of renal cell adenoma or carcinoma (combined) at the highest dose of TFE in both male and female rats compared to controls. See pages 121-124 of IARC Monograph 110 (IARC, 2017). OEHHA should correct this oversight."

Response 22: The fact that tetrafluoroethylene (TFE) has been linked to kidney cancer in rodents is already discussed on page 431 of the draft PHG document.

Comment 23: Referring to p. 142, (2nd paragraph) of the draft PHG document, "OEHHA should have mentioned that Raleigh et al. (2014) conducted a cancer incidence study (1988 – 2008) of the 3M Cottage Grove workforce and calculated hazard ratios (95% CI). For the 188 prostate cancer cases reported by Raleigh et al. (2014) when compared to the referent St. Paul plant (n = 253 cases) in a Cox proportional regression model, the hazard ratios for the four quartiles of increased exposure to cumulative PFOA (ug/m^3-yrs) were: 1.0 (reference); 0.80 (95% CI 0.57, 1.11); 0.85 (0.61, 1.19); 0.89 (0.66, 1.21); and 1.11 (0.82, 1.49). OEHHA also should provide the hazard ratio results for the community worker study by Barry et al. (2013) which consisted of a total of 446 prostate cancer cases that resulted in a 10-year lag exposure analysis for PFOA of HR = 0.99 (95% CI 0.94, 1.05)."

Response 23: Summaries of these two studies are already provided in Table A7.26 of the draft PHG document. In response to this comment, OEHHA also now mentions these two studies in Section 5.7.1 of the second draft PHG document.

Comment 24: Referring to p. 202 (1st paragraph with Figure 6.2.1) of the draft PHG document, "OEHHA's statement that 'although it is unknown how much of this leveling off may be due to decreases in PFOA exposure in the US, similar latency patterns following exposure cessation have been seen for other carcinogens, including smoking (Tindle et al., 2018)' is not supported by the reference cited. The Tindle reference is only about smoking – a well known association where the risk for lung cancer among ex-smokers does decline years after cessation but does not reach the level of nonsmokers. The Tindle 2018 reference, however, is not about 'other carcinogens.' OEHHA should identify these 'other carcinogens' with references. Furthermore, an equally logical explanation, if not more so, is the early detection of latent renal cell cancers detected inadvertently by imaging that was conducted for other reasons. Early detection of prostate cancer by PSA also initially increased the diagnoses of prostate cancer in the early 1990s, but subsequently declined.

Response 24: The statement referred to by the commenter has now been rewritten so that it only includes smoking. OEHHA is aware that the risks in former smokers never reach those in never smokers.

Early detection of renal tumors resulting from the increased use of abdominal CT scans is already mentioned in the draft PHG document (Section 6.2.1).

Comment 25: Referring to p. 203 (Table 6.2.2) of the draft PHG document, "OEHHA provides the exposure category midpoint value (ng/mL) for the four exposure categories listed (2.0, 4.7, 6.4, 17.3). This is misleading because this is not the average value found for the distribution in each of these exposure category ranges. This value is not provided in Shearer."

Response 25: The values referred to by the commenter are labeled as the midpoints so it is not clear how they could be considered "misleading." In response to this comment, a footnote has been added to Table 6.2.2 to indicate that the midpoint values were determined by OEHHA.

Comment 26: Referring to p. 204 (2nd paragraph) of the draft PHG document, "OEHHA states the long half-life of elimination of PFOA indicates a single serum measurement would be sufficient to provide an accurate and precise measurement of a person's long-term PFOA exposure. There continues to be considerable controversy regarding the distribution, calculation, and measurement biases associated with the serum elimination half-lives of PFOA in the human population (Dourson et al. 2020). The OEHHA position of a single PFOA measurement is sufficient is not defensible when measured between 2 and 18 years prior to the diagnosis of the disease. Clearly, if the serum elimination half-life ranges between 0.5 and 2.0 years, a PFOA measurement taken 8.8 years prior to

the diagnosis could be 5+ half-lives casting questions on the relationship between a single PFOA measurement and its relation to the diagnosis of kidney cancer."

Response 26: PFOA is not rapidly eliminated and is therefore stable over a substantial period of time. Even more importantly though, since PFOA was measured using the same methods in all of the participants in the human studies OEHHA used to develop its HPCs, the resulting bias from exposure misclassification is most likely towards the null and not towards the associations seen in these studies. This is true regardless of whether the half-life is 6-24 months or longer.

Comment 27: Referring to p. 207 (Table 6.2.3) of the draft PHG document, "OEHHA must explain why they chose not to include the P_{trend} statistics that were in Shearer et al. (2021) (labeled therein as Table 2). Alternatively it must put the P_{trend} statistics back into the OEHHA abstracted Table 6.2.3. As Shearer explained on page 582 of their JNCI paper, 'we observed statistically significant positive trends in RCC risk with increasing pre-diagnostic conditions of several PFAS, including PFOA (highest quartile vs lowest, OR = 2.63, 95% CI = 1.33 to 5.20) P_{trend} = 0.007' based on intraquartile median value without adjusting for other PFAS. Adjusting for other PFAS, they did not observe a statistically significant P_{trend} with PFOA (highest quartile vs lowest OR = 2.19, 0.86 to 5.61), P_{trend} = 0.13."

Response 27: Confidence intervals and p-values provide similar information. Since the confidence intervals are already presented in Table 6.2.3, it would be redundant to provide p-values as well.

The fact that variance estimates changed (i.e., the confidence intervals widened) after adjusting for other PFAS, and that this was expected, is already discussed in the draft PHG (in the paragraph preceding Table 6.2.3) as well as in the responses to several of the other comments here.

Comment 28: Referring to p. 207 (Table 6.2.3) of the draft PHG document, "In this matched case-control study, according to Shearer et al, the category cut points were assigned based on quartiles of serum concentrations of each PFAS among controls (except for PFUnDA and PFDA). By standard definition the odds ratio of the least exposed category (referent) is set at 1.0. However, there were only 47 cases in this reference group with the least exposure to PFOA (< 4.0 ng/mL). This distribution seems rather odd where there are 81 controls and only 47 cases in the referent group. One would expect more similar distribution among the least exposed. Neither Shearer et al nor OEHHA commented on this referent group which becomes the main driver in the subsequent OR calculations for the other 3 exposure categories."

Response 28: The commenter is correct that the quartile cut-off points in this study were based on the PFOA distribution in controls. However, it is incorrect to say that a more even distribution of cases and controls is expected. Because PFOA was associated with renal cell cancer in this study, the finding of more cancer cases in the

higher quartile and fewer cancer cases in the lower quartile is what is expected and is exactly what the data show (Shearer et al., 2021).

Comment 29: "Steenland et al. (2020) cautioned readers about interpreting data from low exposure contrast studies. This included the Shearer et al. study. OEHHA was no less cautious with low exposure range studies when they discussed with their critique of the Eriksen et al. (2009) study."

Response 29: It is important to not only evaluate whether bias may or may not be present, but also its likely magnitude and direction. As discussed further in the response to Comment 21 from this commenter, this is what OEHHA had done when evaluating the exposure ranges in the Eriksen et al. (2009) and Shearer et al. (2021) studies.

It should also be noted that OEHHA identified several high exposure contrast studies of PFOA and kidney cancer (Vieira et al., 2013; Raleigh et al., 2014; Steenland and Woskie, 2012; Barry et al., 2013), and all but one of these found strong evidence of an association.

Comment 30: "Reverse causation is referred to as a type of pharmacokinetic bias (Andersen et al., 2021a) and occurs when measurement of the physiological outcome (e.g., eGFR) has been moderated by the health outcome itself. It is difficult to understand how Shearer et al. (2021) can infer a disease state that will not be diagnosed until, on average, 8+ more years after a single serum measurement of PFOA, could have influenced that single measurement. OEHHA offers no biological explanation. The pharmacokinetic bias occurs when there is a sufficient window of time for the disease state to influence the measured physiological outcome. In this situation, the lack of an association between eGFR, PFOA, and kidney cancer, is little proof that reverse causation does, or does not, exist. Certainly, it is possible there could be some pre-diagnostic conditions that result in declining renal function but it remains highly speculative for OEHHA (and Shearer et al.) to surmise that the lack of an association between a single eGFR measurement and the diagnosis of kidney cancer eliminates the concern about this pharmacokinetic bias in the association between the exposure (single measurement of PFOA) and kidney cancer."

Response 30: The commenter has not provided evidence or a clear rationale for what they are suggesting here. OEHHA evaluated the possibility of reverse causation and found that it is very unlikely given that serum PFOA concentrations and estimated glomerular filtration rate (eGFR) values were measured many years before cancer diagnosis.

Comment 31: Referring to p. 211 (7th paragraph) of the draft PHG document, "OEHHA states that although no dose-response was presented in Vieira et al. (2013), the ORs for the two highest exposure categories were increased and statistically significant for the relationship between PFOA and kidney cancer. OEHHA did not decide to similarly combine the top two exposure categories in the Steenland and Woskie (2012) cohort mortality study. If they had, the results would not have been statistically significant.

Combining the upper two quartiles in Steenland and Woskie (2012), there were 8 observed kidney cancer deaths and approximately 6.3 expected deaths (SMR = 1.27; 95% CI 0.39 – 1.76) for estimated cumulative exposure of PFOA >= 1500 ng/mL-years. See *infra*, extended comments for Page 214, 3rd paragraph."

Response 31: OEHHA does not state that, "no dose-response was presented" but that, "Formal statistical tests of dose-response like p-trends were not presented…" The fact that the authors did not do a formal statistical test for dose-response does not mean that a dose-response pattern is not present. In fact, an overall trend of higher kidney cancer risks with higher PFOA exposure can be seen in the Vieira et al. (2013) results, and this overall trend is consistent with a dose-response relationship between PFOA and this cancer.

Please see Response 4 to this commenter regarding combining the upper two exposure categories of Steenland and Woskie (2012). OEHHA did not combine the upper two exposure categories in either the Vieira et al. (2013) or the Steenland and Woskie (2012) studies and sees no obvious reason for doing so. The commenter has not provided any strong rationale for doing this either.

Comment 32: Referring to p. 220 of the draft PHG document, "The Vieira et al. (2013) study is an epidemiology, not toxicology, study where OEHHA decided to exclude the top dose category of around 500 ng/mL to enhance model fit and this value was 'well above those seen in the large majority of the US population.' If the latter is the case, then OEHHA also needs to remove the next highest dose 64.70 ng/mL as well as this is also well above the PFOA values seen in the large majority of the US population today. As shown for NHANES, data in 1999-2000 the 95th percentile for PFOA serum concentration was 8.70 ng/mL (95% CI 7.00 – 10.0) and by 2007-2008 the 95th percentile declined to 6.90 ng/mL (95% CI 5.90-7.60). In the NHANES early release of the 2017-2018 data, the 95th percentile for PFOA had declined to 3.77 ng/mL (95% CI 3.17 – 5.07). Therefore, OEHHA should not retain the 64.70 ng/mL data point in the regression analysis of the Vieira et al study. It is well above the 95th percentile of 3.77 ng/mL in the US general population. Both the 500 ng/mL data point and the 64.70 ng/mL data point well exceed the large majority of the US population today. If the two highest Vieira et al. data points are excluded (500 ng/mL and 64.70 ng/mL) then the next highest data point becomes 16.60 ng/mL, which is still nearly 5 times higher than the 95th percentile for PFOA in 2017-2018. Both data points should be removed in data analyses; otherwise OEHHA can be accused of data manipulation. Alternatively, OEHHA should leave all 5 data points to be analyzed from the Vieira et al. study."

Response 32: As shown in Figure 6.2.4 and discussed in the associated text, there is a major improvement in model fit after excluding the highest exposure category of Vieira et al. (2013). This was not the case when the next to the highest dose was also removed. This is now stated in the text associated with Figure 6.2.4 in the second public review draft PHG document.

While the 95th percentile for serum PFOA concentrations in NHANES 2017-18 is 3.70 ng/ml (unweighted), the maximum value is 52.80 ng/ml, which is close to the 64.70 ng/ml data point in Vieira et al. (2013) (NHANES, 2022; Vieira et al., 2013). Although the maximum value in NHANES is only based on a single person, it should be noted that only a small fraction of the entire US population is included in NHANES. For example, while the 2018 US population was 327 million (US Census Bureau, 2018), only 1,929 people (0.0006%) provided serum for PFOA measurements in the 2017-18 NHANES. Because of this, a single value seen in NHANES is likely to represent thousands of people if extrapolated to the entire US population. Overall, the finding of a PFOA serum concentration in NHANES that is close to the 64.70 ng/ml data point in Vieira et al. (2013) suggests that the cancer risks at PFOA exposures near 64.70 ng/ml are directly and highly relevant to many people in the US.

Comment 33: "PFOS should not be considered a carcinogenic agent based on liver tumors observed in rats.

The data OEHHA cites as demonstrating an association between PFOS and liver cancer in rats does not support such a conclusion. Based on the differences in species-specific mechanisms between humans and rodents, however, 3M finds that the Butenhoff study and the other publications, do not support the conclusion that PFOS is carcinogenic to humans."

"3M's review of the established mechanistic data does not lead to the conclusion that PFOS is likely to cause liver cancer in humans. The mechanistic research shows that liver tumors in rats with exposures to PFOS are explained by the activation of several hepatic xenosensor nuclear receptors, such as peroxisome proliferator-activated receptor α (PPARα), constitutive androstane receptor (CAR), and pregnane X receptor (PXR).

The qualitative differences between humans and rodents in the susceptibility of the xenosensor nuclear receptor activation brings into question the relevance of rodent liver tumor response and biological significance, if any, to humans, as it relates to PFOS exposure.

OEHHA acknowledged 'there is substantial debate about whether hepatic effects of PPARα-activating compounds in rodents are relevant to humans due to interspecies differences in activation characteristics.' However, OHHEA ignored these interspecies differences in activation characteristics for CAR and PXR, noting that the uncertainty about whether hepatic tumors are caused 'solely' by activation of PPARα means that evidence of liver tumors in rodents should not be dismissed 'due to the assumption that it lacks human relevance.'

OEHHA's conclusion is *not* supported by the available scientific data because similar to PPARα, detailed mechanistic studies in regards to the hyperplastic responses have also shown a species-specific difference in the functions of CAR and PXR between rodents (more susceptible) and humans (less sensitive).

The significance of the above-mentioned mechanistic data which demonstrated the additional non-PPARα nuclear receptor activation by CAR and PXR in rodents are two-fold:

1) It provides the direct evidence of a plausible biological mechanism in rodents, and

2) It also illustrates a species-specific difference in the functions of these xenosensor nuclear receptors that likely explain why humans are considerably less sensitive to the pleiotrophic effects of CAR and PXR activation than rodents, similar to what PPARα MOA data have shown.

Overall, because PFOS is neither genotoxic nor mutagenic and it does not metabolize, the known species differences between rodent and human strongly support that PFOS-induced hepatic tumors in rodents are unlikely to occur in humans. This is further substantiated by the lack of epidemiological evidence for liver tumors in highly-exposed populations. Therefore, the qualitative differences in the susceptibility of the xenosensor nuclear receptor activation undermine OHHEA's conclusion that PFOS presents a carcinogenic hazard to humans."

Response 33: PFOS was recently listed under Proposition 65 as a carcinogen, following an evaluation by California's Carcinogen Identification Committee using similar evidence provided in the draft PHG. Furthermore, US EPA (2023) recently proposed a Maximum Contaminant Level Goal (MCLG) of 0 ppt for PFOS, due to its carcinogenic hazard. In its review of mechanistic evidence for PFOS carcinogenicity, OEHHA did not conclude that a receptor-mediated MOA would likely be the only MOA, whether through PPARα, PXR or CAR. Rather, a number of MOAs are plausible, as illustrated by the review of Key Characteristics of carcinogens for PFOA and PFOS, included in Section 5.7.3 and Appendix 8 of the draft PHG document. In addition, there is some evidence of PFOS genotoxicity, from multiple positive in vivo genotoxicity studies described in Appendix 8, recognizing there are also in vitro assays and some in vivo studies that show no genotoxic effects. Thus, one cannot exclude a genotoxic MOA for PFOS, just as one cannot exclude a receptor-driven mechanism or other mechanisms. The chosen method for PFOS dose-response analysis consisting of linear extrapolation to a low dose is a default method when the underlying MOA cannot be established with certainty, as is the case for PFOS.

Comment 34: "PFOS should not be considered a carcinogenic agent based on pancreatic islet cell tumor observed in male rats.

PFOS should also not be considered as a carcinogenic agent to humans based on pancreatic islet cell tumor observed in rats. In the same 2-year cancer bioassay for PFOS, (Butenhoff et al., [2012a], the authors did NOT find a statistically significant PFOS treatment-related relationship between PFOS ingestion and pancreatic islet cell carcinoma in male Sprague Dawley rats. The original study (referenced as Thomford 2002 by the OEHHA) also did not find a statistically significant increasing trend in

pancreatic islet adenoma, carcinoma, or combined adenoma and carcinoma. The reason OEHHA concluded '[a]n increase in pancreatic islet cell carcinoma (by trend) was also observed in male rats[,]' was solely due to a different method of calculating the tumor incidence rate."

Commenter's Table 3 compares tumor incidences from Thomford et al. (2002) and from OEHHA analysis.

"As shown, Thomford 2002 calculated the total tumor incidence rate based on the total number of the tissues examined per specific dose group. OEHHA calculated the tumor incidence rate based on the number of animals alive at the time of first occurrence of the tumor."

Response 34: This effective number approach to account for study mortality is a common practice in risk assessment and has been applied in many peer-reviewed OEHHA assessments. Animals that died prior to the date of first tumor occurrence may have had cancer that escaped detection. Alternatively, if not for their earlier deaths (presumably unrelated to cancer pathogenesis), they could have possibly developed cancer if they had lived long enough. Thus, counting these animals as negatives in the tumor incidence estimate would underestimate the true incidence of tumors in the study population. As such, the increase in pancreatic islet cell tumors in male rats was determined to be significant by trend.

Comment 35: "The relationship between pancreatic islet cell tumors and PFOS is further called into question because these tumors are one of the common spontaneous tumor types documented in aged Sprague Dawley rats. While the specific mechanisms are not fully understood, scientists believe that genetic and environmental factors could be involved in tumor growth. For instance, increased dietary calories (i.e., via *ad libitum* food consumption) could contribute to the development of spontaneous age-related tumors in Sprague Dawley rats such as chronic nephropathy, exocrine pancreatic atrophy and fibrosis, pancreatic islet hyperplasia and fibrosis, and the early development of potentially lethal tumors in the pituitary and mammary glands.

In the 2-year cancer bioassay study for PFOS where food was given *ad libitum*, Butenhoff et al. 2012 reported that the control and K^+PFOS-treated male rats had generally similar food consumption rates. However, there were intermittent lower body weights observed in the 20 ppm-treated group animals. While the actual metabolic caloric balance was not evaluated in that study, it is possible that the subtle difference in food consumption per body weight may have, in part, contributed to the observation of intermittent lower body weights."

Response 35: The commenter suggests that increased calories could contribute to the development of spontaneous age-related tumors but observes that there were intermittent lower body weights in the high dose group. Since decreased body weights likely reflect decreased (and not increased) caloric intake, the proposed mechanism is unclear and lacks plausibility.

Moreover, intermittently decreased body weights (at 53 weeks) were observed in female rats only, while the OEHHA tumor analysis of Butenhoff et al. (2012b) data is based on observations in male rats.

Comment 36: "In addition, the pancreatic islet cell tumor type (endocrine-based) should not be confused with the pancreatic acinar cell tumor (exocrine-based) that has been reported in rats with exposure to PFOA. The MOA of the pancreatic acinar cell tumors in the rats exposed to PFOA is likely through increased cholecystokinin ('CCK') as a consequence of cholestasis. While CCK promotes acinar cell hyperplasia in the rats, this MOA is not considered to be relevant to human risk. In humans, the causal mechanism in the development of the human pancreatic (ductule) adenocarcinomas is neurogenically dependent, rather than the CCK pathway, as observed in rodents."

Response 36: OEHHA does not directly compare pancreatic tumors caused by PFOA and PFOS or draw any conclusions that would be based on such a comparison.

The cholecystokinin-dependent mechanism of pancreatic cell proliferation and tumor formation is discussed in detail in Section 5.7.3. This mechanism involves PPARα activation. The conclusion of the discussion is as follows: "Without additional experimental evidence linking pancreatic and testicular tumors in rodents solely to PPARα activation, OEHHA concludes that there is no scientific basis to exclude these tumor types for evaluation of human cancer risk." The commenter did not present any new evidence that could affect this discussion or resulting conclusions.

In the absence of a clearly established mechanism of carcinogenesis, concordance of tumor sites between animals and humans is not necessary (US EPA, 2005). Given all the mechanistic evidence for PFOA carcinogenesis analyzed in the draft PHG document, the cholecystokinin-dependent MOA is not likely to be the sole cancer MOA. Thus, it is not necessary to consider mechanisms of site-specific carcinogenesis, and specifically the MOAs for human pancreatic adenocarcinomas.

Comment 37: "Collectively, these data clearly illustrate why PFOS should not be considered as a carcinogenic agent based on either liver tumor or pancreatic islet cell tumor observed in rats. Several regulatory bodies have also reached similar conclusions, including:

> **USEPA, 2016**
>
> *In the case of PFOS, the existing evidence does not support a strong correlation between the tumor incidence and dose to justify a quantitative assessment.*
>
> **Health Canada, 2018**
>
> *Some associations between PFOS and risk of cancer… were observed; however, the evidence does not support the carcinogenicity of PFOS.*
>
> **EFSA, 2020**

> *In the Opinion on PFOS and PFOA (EFSA CONTAM Panel, 2018), a number of studies on cancer incidence or cancer mortality at occupational or environmental exposure were reviewed. In summary, those studies provided insufficient support for carcinogenicity of PFOS and PFOA in humans.*"

Response 37: In its literature analysis and hazard identification for PFOS, OEHHA considered these three assessments (EFSA, 2020; Health Canada, 2018; US EPA, 2016b). After the release of these assessments, several relevant studies, e.g., some finding positive genotoxic activity in vivo, have been published (for example, NTP, 2019b and Eke et al., 2017). In its deliberations, OEHHA used all available data, and the resulting conclusions may differ from those of other agencies. As mentioned in the response to this commenter's Comment 33, PFOS was recently listed under Proposition 65 as a carcinogen, following an evaluation by California's Carcinogen Identification Committee using the same evidence provided in the draft PHG. To summarize the most recent assessments of PFOS:

US EPA (2023)

> "Consistent with the *Guidelines for Carcinogenic Risk Assessment* (USEPA, 2005), EPA reviewed the weight of the evidence and determined that PFOS is *Likely to Be Carcinogenic to Humans*… This determination is based on the evidence of hepatocellular tumors in male and female rats, pancreatic islet cell carcinomas in male rats, and mixed but plausible evidence of bladder, prostate, kidney, and breast cancers in humans."

California Carcinogen Identification Committee (2021)

> The Committee determined that PFOS and its salts and transformation and degradation precursors were clearly shown through scientifically valid testing according to generally accepted principles to cause cancer (8 yes, 2 no, 1 abstain).[4]

IARC (in Zahm et al., 2023)

> "PFOS was classified as 'possibly carcinogenic to humans' (Group 2B) based on 'strong' mechanistic evidence. The evidence for cancer in experimental animals was 'limited' for PFOS, and the evidence regarding cancer in humans was 'inadequate.'"

While the commenter suggests that "PFOS should not be considered as a carcinogenic agent," the quote from the US EPA (2016b) document refers to a lack of justification for a quantitative assessment (based on observed tumors at just one dose). This is not the same as stating that PFOS is not a carcinogen. The most current US EPA evaluation, cited above, identifies PFOS as "likely to be carcinogenic to humans."

[4] https://oehha.ca.gov/media/downloads/crnr/120621cictranscript.pdf

Similar to other assessments (EFSA, 2020; Health Canada, 2018; IARC, 2023), OEHHA did not find consistent evidence of PFOS carcinogenesis in human epidemiological studies, as described in section 5.7.1 of the PHG draft. OEHHA's decision to analyze PFOS as a carcinogen is based primarily on animal and mechanistic evidence, described in detail in the PHG draft document.

Comment 38: "A quantitative assessment for PFOS carcinogenicity based on the available data is not supported. 3M recommends that OEHHA reconsider its approach on cancer assessments for PFOS."

Response 38: As outlined in Responses 33-37, objections raised by the commenter have already been addressed by OEHHA in its considerations of PFOS hazard characterization and dose-response. From the Butenhoff (2012) studies, statistically significant tumors were observed in both sexes, and significant trends were observed. Because of this, OEHHA judged the carcinogenicity data of PFOS to be sufficient.

Comment 39: "There is insufficient evidence to explain the underlying reasons for an epidemiological association with increased total cholesterol and PFOS.

OEHHA considered four cross-sectional studies (Dong et al. 2019); Steenland et al. (2009); Frisbee et al. (2009); and Starling et al. (2014) in their determination of a PHG and PHC for PFOS based on increased serum total cholesterol in the human. 3M believes the use of these studies, and particularly Steenland et al. (2009) study to evaluate an HPC is highly premature given recent scientific literature, which OEHHA did not consider. Recent studies include two workshop panel reports, published in 2021 (Fragki et al., 2021; Andersen et al., 2021), that related to the question what might be the underlying reasons why many epidemiological studies, primarily cross-sectional, have reported positive association between serum concentrations of perfluoroalkyl substances (in particular PFOS, PFOA, PFHxS) and modestly elevated serum cholesterol. In addition, the recent scientific opinion by a regulatory body, EFSA, also did not consider this association (observation of increased cholesterol with PFAS in humans) to be a driver in its calculation of a TWI because of the uncertainties that have recently arisen in the literature. More recently, Dzierlenga et al. (2021) reported an association with increased dietary fiber and decreased PFAS levels using NHANES data. Dietary fiber is known to reduce serum cholesterol levels. This raises the question, which was not examined in the four studies evaluated by the OEHHA (Dong, Steenland, Frisbee, or Starling) as to the confounding presence of dietary fiber in studying the association between PFOS/PFOA and serum total cholesterol.

Because of the timing of their publications, it is understandable the OEHHA may not have been aware of these recent publications. 3M recommends that OEHHA devote sufficient resources to more thoroughly understand the pharmacokinetics and mechanisms concerning the association between lipids and PFOA, as recommended by the two workshop panels (Fragki et al. 2021 and Andersen et al. 2021) before issuing a HPC based on such an association.

3M is not aware of other state, federal, or international regulatory agencies that have chosen to use the Steenland et al. (2009) cross-sectional study on PFOS and lipids as their Point of Departure to calculate a health-based guidance value. We are not aware of any regulatory agency that has declared a causal association between low concentrations of PFAS and modestly elevated serum total cholesterol. Many of the questions raised by others (Fragki et al. 2021; Andersen et al. 2021; EFSA 2020; ATSDR 2021; Dzierlenga et al. 2021; Chang et al. 2017; and Canova et al. 2020) need to be addressed for further elucidation of this epidemiologic association. Thus, there is insufficient evidence of an association with cholesterol in humans at general population levels, to warrant it as a POD for the calculation of a PHG for PFOS by OEHHA.

To assist OEHHA with its review of more recent literature, 3M provides the following summaries of published papers and reports to OEHHA's attention, including a list of excerpts from the two workshop panels (Fragki et al. 2021 and Andersen et al. 2021b) for OEHHA's consideration."

Response 39: The Andersen et al. (2021) publication, funded by 3M, presents hypotheses and opinions regarding PFAS effects on lipids. A full evaluation of the literature and resulting causal inference is not included. The authors present four major hypotheses that may explain the associations seen between PFAS and increased serum lipids:

- A true causal effect;
- reverse causality;
- confounding by disease; and
- "pharmacokinetic bias."

Overall, the authors indicate that there is little evidence for either reverse causality or confounding by disease, and provide good evidence against both (e.g., statins do not reduce serum PFAS concentrations; adjustments for kidney disease had little impact on PFAS-lipid associations). With regard to "pharmacokinetic bias," the authors present several pieces of evidence that this bias did not occur (e.g., ezetimibe inhibits cholesterol uptake into enterocytes but does not affect PFAS serum concentrations), and provide no direct evidence that it does occur. The authors hypothesize that serum PFAS-lipid associations might be caused by a common dietary constituent that increases the excretion of both lipids and PFAS. However, no specific dietary factor is proposed and no supporting evidence is provided. Overall, while this publication offers some interesting thoughts, it does not provide any substantive arguments on PFAS-lipid associations beyond those issues already covered in OEHHA's PHG document.

The primary focus of Fragki et al. (2021) is on possible mechanisms of PFAS toxicity and related pharmacokinetic differences between laboratory animals and humans. This paper provides no additional data or analyses for evaluating causal inference beyond the information in the PHG document. Conclusive evidence for any of the proposed

mechanisms is not given, and a convincing argument that PFAS do not increase serum lipids is not made.

The European Food and Safety Authority (EFSA) expressed concern that PFAS-serum cholesterol associations might be due to a common enterohepatic cycling of PFAS and bile acids (EFSA, 2020). However, the document provides no supporting evidence. OEHHA performed an in depth analysis of this issue (summarized in Section 6.1.2 of the draft PHG document), comprehensively reviewed the relevant research, and found this proposed mechanism to be highly unlikely.

Dzierlenga et al. (2021) found that while increased fiber intake seems to be associated with lower serum PFOS concentrations, this association is not very strong. Because of this, fiber intake is unlikely to have caused the PFOS-serum lipid associations reported in many of the studies OEHHA reviewed. For example, the difference in serum PFOS concentrations between the lowest and highest quartiles of fiber intake in Dzierlenga et al. (2021) was about 15%. In contrast, the difference in serum PFOS concentrations between the highest and lowest quartiles in Steenland et al. (2009b), the study OEHHA used to calculate its noncancer HPC, was 515%, >34-times larger (Steenland et al., 2009b). Given this large difference, any claim that fiber was a major confounder based on the Dzierlenga et al. (2021) findings is mostly implausible (Axelson, 1978).

Finally, the concerns expressed by Canova et al. (2020) and ATSDR (2021) (reverse causality, confounding, lipoprotein binding, enterohepatic reabsorption, seemingly small effect sizes) are already addressed in Section 6.1.2 of the draft PHG document. It should also be noted that neither of these publications provided evaluations of causal inference that were as extensive or thorough as those presented in the draft PHG document.

Comment 40: Referring to pp. 88 and 98 of the draft PHG document, “It is unclear why the study by Chang et al. 2017 was included in Table 5.2.3 (a table animal studies of liver effects) but excluded from Table 5.3.2 (a table of animal studies that reported lipid effects). See detailed comments below regarding the Chang et al. 2017 study as related to the findings from Steenland et al. 2009.

In their study, Chang et al. administered a single K+PFOS dose (9 mg/kg) to a low-dose group (n = 6/sex) or 11-18.2 mg/kg K^+PFOS on 3 occasions to a high-dose group (n = 4- 6/sex). Scheduled blood samples were conducted on all monkeys prior to, during, and after administration for up to 1 year. They were analyzed for PFOS concentrations and clinical chemistry markers including serum lipids. When compared with time-matched controls, PFOS administration did not result in any toxicologically meaningful or clinically relevant changes in serum clinical measurement for coagulation, lipids, hepatic, renal, electrolytes and thyroid-related hormones.

Chang et al. did report a slight reduction in serum cholesterol (primarily HDL). Using a Bayesian approach, Chang et al. implemented Monte Carlo Markov Chain techniques and calculated a corresponding lower-bound 5th percentile benchmark concentrations

($BMCL/_{1sd}$) of 74,000 and 76,000 ng/mL for male and female monkeys, respectively, based on the slight reduction in HDL. Compared to the 2013-2014 geometric mean serum PFOS level of 4.99 ng/mL from NHANES, this amounted to a 4 orders of magnitude margin of exposure. Therefore, the obvious striking contrast between Chang et al. cynomolgus monkey results, and the 16.4 ng/mL LOAEC for increased cholesterol (identified by OEHHA from the Steenland et al. 2009 study) as shown in Table 6.1.13 by OEHHA, should be addressed by OEHHA."

Response 40: In response to this comment, the Chang et al. (2017) study results for total serum cholesterol and HDL are now included in Table 5.3.2.

In this study, reductions of 4-12% in serum cholesterol and HDL were reported, but no statistical significance of these findings was presented. In fact, it is likely that results are not statistically different from the background given the small sample numbers and overlapping standard deviations on the graph.

As described in the PHG draft document, the current epidemiological literature provides evidence that PFOA and PFOS can cause increased total cholesterol in humans, while some animal studies have shown decreased total cholesterol with PFOA and PFOS exposure. These species differences may be due to the stronger activity of PPARα in animals. Thus, the endpoint of decreased cholesterol in animal studies would not be fit for extrapolation to humans, since the direction of effect is opposite and different underlying mechanisms are likely. Therefore, the Steenland et al. (2009b) epidemiological study should not be directly compared to the animal data.

Comment 41: Referring to pp. 105, 194, and 196 of the draft PHG document, "OEHHA writes about cross-sectional studies being 'frequently criticized based on their potential for reverse causation.' OEHHA appears to be confusing concepts of reverse causation with temporality. One of the primary criticisms of cross-sectional studies is that they cannot assess temporality – *i.e*., did the exposure precede the condition being studied. We refer OEHHA to a paper on pharmacokinetic bias that can occur from either confounding or reverse causation (Andersen et al. 2021a) that provides both PFAS and non-PFAS examples. In their workshop, Andersen et al. (2021b) examined reverse causality as one of their 4 hypotheses but this has to do with the possible mechanism of incorporation of PFAS into cholesterol containing particles such as LDL. PFAS would then increase proportionally with the LDL. OEHHA acknowledges that the major transport proteins for cholesterol in the blood are the lipoproteins (not albumin). OEHHA dismisses PFAS binding to lipoproteins because of the results from Butenhoff et al. 2012. While this one study investigated the issue, it was based on a blood sample from only one individual and cannot reasonably be relied upon to support the conclusion OEHHA attempts to draw. Andersen et al. also briefly mentioned the co-distribution – hypothesis."

Response 41: OEHHA has not confused the terms "reverse causality" and "temporality," and uses the former in the exact same manner it is used in the publication cited by the commenter (Andersen et al., 2021). The publication cited by the commenter

did not involve original research. It defines pharmacokinetic bias as either reverse causation or confounding, both of which are already extensively evaluated in the draft PHG document. The Andersen et al. (2021) publication does not discuss associations between PFAS and serum lipids, and provides no specific argument why the physiologically-based pharmacokinetic modeling and simulations it proposes would add any significant insight into evaluating these particular findings. In fact, the methods proposed by the authors can be associated with a number of significant weaknesses (e.g., uncertainties in model validation, the use of unverified model assumptions, differences between animals and humans, the use of simulations vs. real data, lack of known mechanisms, and so on), and these weaknesses are acknowledged by the authors throughout the publication.

The Butenhoff et al. (2012) study was only one of many pieces of evidence supporting the causal relationship between PFAS and increased serum lipids. A significant amount of other evidence is available, and this is presented in Section 6.1.2 of the draft PHG document.

Comment 42: Referring to pp. 104, 105, and 193 of the draft PHG document, “OEHHA discusses possible sources of dietary confounding but considers it unlikely. OEHHA then concentrates on adjustments for fat, total calorie, meat and vegetable intake but never considered dietary fiber as a potentially confounding factor. While the Support Document states that no major confounding has been identified related to the Steenland et al. 2009 study (page 193), it acknowledges that consumption of a high fat diet or high total caloric intake could potentially be related to total cholesterol and PFOS exposure, although both could be in the causal pathway. Both high fat or high total caloric intake were strongly related to factors that were controlled for in the Steenland et al. study (BMI, smoking, and exercise), and therefore according to the authors were unlikely to have been ‘fully’ responsible for the PFOS and total cholesterol association in the study. Not discussed by OEHHA, however, is the possible confounding effect of fiber intake. Dzierlenga et al. (2021) suspected consumption of dietary fiber can be a confounding factor in an association between PFAS and serum cholesterol because dietary fiber is inversely related with dietary cholesterol and may decrease PFAS levels through increased gastrointestinal secretion.

Analyzing dietary survey data from NHANES data 2005-2006 through 2015-2016 among 6,482 adult participants (20 – 79 years of age), which consisted of two 24-hour diet recalls, Dzierlenga et al. derived nutrient intakes, including an index for total dietary fiber. The calculated median fiber intake of 16g/ was consistent with other data reported in the United States. Dzierlenga et al. calculated the percent difference in PFAS concentration per interquartile range increase in fiber with the NHANES sampling parameters used to make the results generalizable to the U.S. Thus, the adjusted percent difference in PFOA, PFOS, and PFNA, per interquartile increase in fiber was -3.64%, -6.69%, and -8.36%, respectively. Dzierlenga et al. suggested their analyses indicated that dietary fiber increases the gastrointestinal excretion of PFOA, PFOS, and PFNA in humans. Although this was less than a 10% difference in PFAS with IQR difference in dietary fiber, Dzierlenga et al. suggested these findings may be important

in those studies of health outcomes where the outcome-PFAS association is also modest."

Response 42: Please see the response to Comment 39 from this commenter regarding potential confounding by dietary fiber.

Comment 43: Referring to p. 191 (Table 6.1.16) of the draft PHG document, "It is a critically important often overlooked point, including in the Support Document, that Steenland et al. 2009 noted on page 1276 of their paper that, 'although PFOA and PFOS were highly significant predictors of lipid levels (their study had high power to detect statistically significant differences compared with prior smaller studies), the perfluorinated compounds themselves did not explain a large portion of the variance in lipids. For total cholesterol, the most important predictors were age, gender, and body mass index, not serum levels of PFOA or PFOS.' 3M is unable to find the actual percent of variance of lipids that were actually explained by PFOA or PFOS in the Steenland et al. paper, nor could this information be found in the C8 Science Panel's probable link statements regarding this particular research. This contributes to the fact that the association between total cholesterol and PFOS was quite modest, despite its statistical significance as a result of the sample size. Given the associational relationship is modest at best, OEHHA should revisit its analysis regarding the PFOS POD."

Response 43: A finding that PFOS is not the primary determinant of serum lipid levels is not surprising since a large number of other factors influence these outcomes. And, a finding that PFOS is not the primary cause of high total cholesterol (TC) does not mean that is not a cause (or a preventable cause) of high TC. Please see the responses to the similar comments regarding R^2 values above (Responses to Comments 14 and 17 from this commenter).

Comment 44: Referring to p. 193 (1st paragraph) of the draft PHG document, "The Support Document states that 'while the relatively small changes in mean TC levels seen with increasing PFOS exposure levels may not affect many people, on an individual basis, the population effects of these small changes, given that TC is a major risk factor for cardiovascular disease, are likely to be widespread and large.' If that were true, then the C8 Science Panel would have observed some level of association in the community. They did not. Nor did the C8 Science Panel declare a probable link with heart disease (see above)."

Response 44: Given the magnitude of the odds ratios between PFOS and high TC seen in the C8 area (i.e., odds ratios of 1.14 to 1.51), the increased relative risk of cardiovascular disease associated with these particular effects would be expected to be relatively small (e.g., odds ratios <1.2). Given this, it is not clear that Winquist and Steenland (2014), even with its large sample size, had sufficient statistical power to detect this level of effect. This is especially true given all of the potential biases or confounders that could have affected this study, and the fact that even small biases or small degrees of confounding can have major effects when increases in relative risk are small (Hill, 1965; Axelson, 1978). Given all of this, it might be tempting to argue that if

the PFOS-related increases in cardiovascular disease are expected to be small then they should be considered unimportant. However, since heart disease is the number one cause of death in the US, even small increases in this outcome are likely to represent very large numbers of adversely affected people.

Comment 45: Referring to p. 193 (3rd paragraph) of the draft PHG document, "The referenced studies by Canova et al. (2020) and Li et al. (2020) are both cross- sectional studies of the Veneto (Northeastern Italy) and Ronneby, Sweden regions. While these studies report an association between cholesterol and PFOS (and PFOA, PFHxS) neither addressed, with data, the methodological questions raised by Fragki et al. and Andersen et al. It should be noted that Tony Fletcher was a co-author of the Canova et al. and Li et al. papers, too, as he was with Fragki et al. (2021) and Andersen et al. (2021). The discussion section in the Canova et al. paper mirrors much of what Fragki et al. (2021) and Andersen et al. (2021) have written. In this regard, there is a consistency of findings on what needs to be done. Canova et al. (2020) concluded, 'More effort is needed to study mechanisms of action of PFAS in human cells and tissues to understand potential causality, and longitudinal studies of cardiovascular risk in relation to PFAS, particularly lipid subfractions, are warranted.' The Li et al. (2020) paper reiterated its other limitations, including information on cholesterol-lowering medications, dietary habits, and socioeconomic status, all of which affect serum lipids and are potential confounders if they happened to be associated with PFAS levels."

Response 45: Li et al. (2020a) and Canova et al. (2020) are only two of many studies that have reported links between PFOS and serum lipid levels. The others are reviewed in Section 5.3.1 of the draft PHG document. As noted above, the concerns expressed by Canova et al. (2020) (reverse causality, confounding, lipoprotein binding, enterohepatic reabsorption) have already been addressed in Section 6.1.2 of the draft PHG document, and these authors provide only a very limited evaluation of causal inference. Although Li et al. (2020a) expressed concerns about lipid lowering medications, dietary habits, and socioeconomic status, they did not present any detailed explanations, research, or quantitative evaluations justifying these concerns. And, while information on these three factors were not available in the Li et al. (2020a) study, they were available in a number of other PFOS-lipid studies (Averina et al., 2021; Canova et al., 2020; Dong et al., 2019; Fisher et al., 2013; Geiger et al., 2014; Jensen et al., 2020; Lin et al., 2019; Skuladottir et al., 2015; Steenland et al., 2009b; Yang et al., 2021; Zeng et al., 2015; Frisbee et al., 2010). Overall, OEHHA found no evidence that cholesterol lowering medications, dietary habits, or socioeconomic status caused major bias or confounding.

Comment 46: Referring to p. 194 (2nd paragraph) of the draft PHG document, "While it is true that approximately 80% of the community participated in the C8 Health Project, the Steenland 2009 study never addressed the question of nonresponse bias. Thus, it is somewhat misleading for OEHHA to say there is no obvious selection bias because it was never examined."

Response 46: A response rate of 80% is quite high for a large high quality study like this, and this high rate is a very good indication that major selection bias is unlikely.

Comment 47: Referring to p. 194 (3rd paragraph) of the draft PHG document, “As discussed above, reverse causality is only one type of pharmacokinetic bias and that does not mean there is the absence of confounding or shared co-distribution (e.g.., enterohepatic circulation) between PFOS and some other factor that confounds the association between PFOS and cholesterol.”

Response 47: OEHHA agrees that reverse causality and confounding are not the same and as such has evaluated each separately (please see Section 6.1.2 of the draft PHG document).

ASSOCIATION OF CALIFORNIA WATER AGENCIES

Comment 1: "Please consider the following while finalizing this PHG ahead of the development of an MCL by the State Water Resources Control Board (State Water Board).

A. Public water agencies will be required to report exceedances of substances for which no regulatory standard exists. Public water agencies are tasked with the essential element of effective and factual communication with the public to maintain trust with their communities. PHGs are required to be reported in annual consumer confidence reports (CCR's) along with MCLs – sometimes creating confusion and concern. The currently proposed PHGs for PFOA and PFOS might raise concerns from consumers who are unsure what they mean for the safety of their water.

B. Public water systems seek to uphold PHGs that protect public health, are effective, and feasible to comply with while keeping water affordable for customers towards development of an effective MCL.

C. Public water agencies must also prioritize the Human Right to Water, which is often impacted by the increased cost threshold of complying with new MCLs. Water systems that are ineligible for or unsuccessful in obtaining financial support from the state have difficulty preventing increased burdens on already socioeconomically disadvantaged communities. Per the State Water Board, the average cost of water increased by 45% between 2007 and 2015. This has already forced low-income households to make difficult household decisions about water consumption to balance other expenses."

Response 1: PHGs are health-based values, and their derivation is guided by Health and Safety Code Section 116365. Considerations other than those of human health cannot be and should not be incorporated into PHG derivation. Otherwise, the public may not be well informed regarding the health effects of exposure to PFOA and PFOS. The listed comments are legitimate concerns that would be best addressed by the Water Board and other agencies that develop and enforce regulatory levels for pollutants in California drinking water.

Comment 2: "OEHHA should continue to follow the regulatory framework for developing PHGs and work with the State Water Board to follow the regulatory framework to develop MCLs.

Consistent with ACWA's previous comment letter, we encourage that OEHHA to continue to make use of additional resources as they become available to inform the assessment of health risk effects of PFOA and PFOs in setting these PHG which will in turn increase the accuracy of the future recommended MCLs. OEHHA and the State Water Board Department of Drinking Water should continue to develop and provide clear communication about the meaning and purpose of PHGs which are complex and can be difficult for the public to understand.

As new information and epidemiological studies become available and potential health risks are better understood, OEHHA should maintain a regular review and update process for PHGs. For example, Table A5.1 in Appendix 5 suggest that food is a much more prominent source of PFOA exposure than water, but the PHG for PFOA acknowledges that there is not sufficient data to determine the impact that food packaging and nonstick cookware have on human exposure to PFAS. As information on this exposure route is developed, OEHHA should reexamine these PHGs.

Consistent with ACWA's prior comments on previous PHG and MCL rulemakings, ACWA supports the development of PHGs based on the risk assessment of public health impacts from studies that are grounded in sound, credible science and research, are well-documented, and collect and analyze current, data and information. OEHHA should adhere to the best available, peer-reviewed practices, principles, and methods used by epidemiological professionals, including U.S. EPA's risk assessment team. As referenced in the past ACWA comment letter regarding development of this PHG, the PHG should be established using studies that reflect human consumption of PFAS-contaminated drinking water, exposure routes in tap drinking water, drinking water consumption, and grouping PFAS compounds in groups based on shared and common health risk indicators."

Response 2: OEHHA acknowledges the comment. The PFOA and PFOS draft PHGs are based on sound science and were developed using the most current principles, practices, and methods for risk assessment. Grouping PFAS chemicals that are similar in toxicokinetic and toxicological properties in humans is one option that OEHHA is exploring. Health and Safety Code section 116365 mandates that OEHHA reviews PHGs every five years, and any new information that becomes available will be considered as part of the review process.

CALIFORNIA-NEVADA SECTION OF THE AMERICAN WATER WORKS ASSOCIATION

Comment 1: "Drinking water providers depend on OEHHA to determine a baseline health-protective level of constituents that may be found in water sources. With so many PFAS already found in the environment, the regulation of these chemicals will have profound impacts on water utilities and water affordability. It is therefore crucial for OEHHA to consider all available, credible health effects data using strictly scientific methods for making its determination of a safe level of acute or chronic exposure to the substance. We believe the peer review OEHHA has invited during this public comment period is important, to validate (and to correct if necessary) OEHHA's process and derived draft PHGs for PFOA and PFOS. More research is likely to reveal new information on the effects of PFAS in the human body, and we strongly encourage OEHHA to invest whatever time and resources are needed to gain the best possible understanding."

Response 1: OEHHA acknowledges the comment, and agrees that peer-review is an important process to ensure that the methods and conclusions reached in the PHG are scientifically sound.

Comment 2: "Besides California, about 30 other states are making their own decisions about human health risk and setting different drinking water standards, setting up an inexplicable muddle. As states move ahead of U.S. EPA and set different regulatory limits on these and other PFAS, it confuses the public and leaves water systems with a nearly impossible communication challenge to maintain the public's trust. We would prefer to see California wait for a consistent nationwide determination from U.S. EPA, but in going ahead of that, OEHHA should consider the health effects conclusions made by other states and explain how OEHHA's toxicological analysis for PFOA and PFOS differs, and why."

Response 2: OEHHA develops its own risk assessments for pollutants in drinking water and keeps abreast of the science used by other states and the US EPA, although the guidelines for risk assessment can differ among federal and state regulatory agencies. The draft PHG lists select state regulatory or advisory levels in Table 8.1. Most of these values are higher than the proposed PHGs because they were based on noncancer endpoints. The US EPA interim health advisories, also included in Table 8.1, are lower than OEHHA's draft PHG values due to different critical studies and differences in toxicokinetic approaches.

Comment 3: "Our members have concerns about the limited laboratory capacity for analysis at extremely low levels, such as 0.007 parts per trillion (ppt) PHG for PFOA. Testing is difficult and expensive. Analytical laboratory capacity must be available, but currently is very limited. Water utilities must publicly report an exceedance of the PHG in their source water. They will need guidance and practical rules on these substances for purposes of the Detection Limit for Reporting. Should they list results as "Non-

Detect" (ND) if test results are at or above the Minimum Detection Level but less than the Consumer Confidence Report Detection Level ("CCRDL")?"

Response 3: OEHHA defers questions regarding analytical methods and reporting requirements to the Water Board. These questions are outside the scope of PHG development.

Comment 4: "One final concern is the specific, and exceedingly low PHG proposed due to carcinogenicity. EPA typically uses Maximum Contaminant Level Goals (MCLGs, analogous to a PHG) of zero ("0") for carcinogenic effects. A PHG value at fractions of a nanogram (e.g. 0.007 ppt) may misrepresent the state of analytical capability. The effect will be to further muddle communication of risk because that value is so low and sources of PFOS, PFOA and other PFAS compounds are found at much higher levels from other sources (e.g. textile coatings, air, food, and so on). We question the use of such a low point, as opposed to zero, and think the reason and effects of using that specific value should be fully explained in plain English."

Response 4: While US EPA generally established MCLGs of 0 for non-threshold carcinogens, the agency also typically provides the concentration in water associated with a 10^{-6} cancer risk for the pollutant in question (see details in US EPA's 2022 PFOA interim health advisory document). PHGs are non-regulatory levels and are not meant to match current analytical methodologies. In contrast, MCLs are regulatory standards that are established as close as feasible to PHGs, but also take other factors into consideration, such as detection limits. Considerations of exposure to PFOA and PFOS from other types of environmental media than drinking water are included in the determination of the relative source contribution (RSC) in PHG calculation.

THE AMERICAN CHEMISTRY COUNCIL (ACC) ET AL. [5]

Comment 1: "The Office of Environmental Health Hazard Assessment (OEHHA) has proposed public health goals (PHGs) for perfluorooctanoic acid and perfluorooctane sulfonic acid (PFOS) of 0.007 parts per trillion (ppt) and 1.0 ppt, respectively, based on evidence of carcinogenic potential. The PHG proposed for PFOA is based 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 of questionable relevance to human risk assessment. In addition, OEHHA has not established a plausible biological basis for concluding that PFOA or PFAS cause cancer. 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 (BMD) methodology. 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."

Response 1: Specific points outlined in this summary are addressed in Comments and Responses below.

Comment 2: "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 (US EPA, 2005). 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."

Response 2: As in the US EPA (2005) Guidelines for Carcinogen Risk Assessment, OEHHA gives greater weight to human data than animal data when high quality human studies are available. As detailed in the draft PHG document, several high quality studies were available for PFOA, and the issues raised by the commenter (exposure, confounding, sample size) have all been addressed. As noted above in response to

[5] Joint submission of the ACC and the Metal Finishing Association of Southern California, Metal Finishing Association of Northern California and California Food Producers

Comment 11 by 3M, site concordance across species is not required to make strong conclusions regarding the carcinogenic effects of chemical exposures in humans.

Comment 3: "The subjects [in Shearer et al. (2021)] had baseline serum collected during 1993-2002, although the samples were not analyzed for PFOA and other PFAS until 2018. These measures were used to back-calculate exposure estimates by OEHHA - not by Shearer et al. (2021)."

Response 3: OEHHA used the PFOA serum measurements as they were presented by Shearer et al. (2021) and did not "back calculate exposure estimates."

Comment 4: "The researchers [Shearer et al. (2021)] calculated odds ratios (ORs) for exposure quartiles and for continuous factors exposure, controlling for multiple potential confounding in addition to the case-control 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 analyses for exposure-response trends."

Response 4: The commenter provided no evidence or analysis to support the contention that assigning quartiles based on the PFOA serum distributions in the controls in the Shearer et al. (2021) study would "skew the analyses for exposure-response trends."

Comment 5: "Unfortunately, it is unclear whether the covariates [in Shearer et al. (2021)] were addressed one at a time (varying each potential confounder, to see how the fit of the model changed) or all at once. No equation was presented in Shearer et al. (2021) to help understand their view of the interactions of all the confounders present when assessing the correlations with RCC."

Response 5: No evidence of why this issue is likely to result in erroneous odds ratios, especially odds ratios as high as those reported in Shearer et al. (2021), are provided in this comment. Shearer et al. (2021) has been extensively peer-reviewed, and the statistical analysis was performed by the US National Cancer Institute.

Comment 6: "As shown in Table 1 and as emphasized with shading, the data [from Shearer et al. (2021)] do not support a positive dose-response relationship (CI includes 1.0) and would be considered not significantly elevated 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. Given the lack of a significance after adjusting for exposure to other PFAS, it is not clear why OEHHA would use the ORs for the exposure quartiles (prior to adjusting for other PFAS) in calculating the cancer slope factor for the study."

Table 1 from Comments: Odds ratios and 95% confidence intervals (CIs) evaluating PFOA serum concentration and risk of renal cell carcinoma (Shearer et al. 2021).

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[7]			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.

Response 6: Basing conclusions solely on p-values is an approach that can be fraught with errors (Greenland et al., 2016). Regardless, the data in the table presented above are important because they demonstrate that the relationship between PFOA and renal cell carcinoma (RCC) was not confounded by other PFAS. The fact that the odds ratios with and without adjusting for other PFAS were only slightly different is good evidence that confounding by these other PFAS did not occur. The key point here is to examine the odds ratios themselves. Basing major conclusions on whether or not the confidence intervals or p-values changed before and after these adjustments is inappropriate. This is because of multi-collinearity: the fact that entering correlated variables into the same regression model will result in a loss of precision (and therefore widen confidence intervals and raise p-values). Importantly, if the other PFAS were shown not to cause confounding (which was the case), then entering them into the final PFOA-RCC models is unnecessary. And, removing them will reduce the problems caused by multi-collinearity. For these reasons, the PFOA-RCC regression models that do not include the other PFAS are the most appropriate ones for evaluating the true cancer risks of PFOA, and these are the ones OEHHA used to develop its PHG.

Comment 7: "Although the OR for the continuous exposure analysis [of data from Shearer et al. (2021)] was statistically significant, questions remain about the meaning of this finding. Of primary concern is whether the single serum measurement taken prior to RCC diagnosis (1993-2002) is an appropriate measure of PFOA exposure. OEHHA reasons that the serum samples taken between 1993 and 2002 from the cases and controls in the Shearer et al. study represent a peak exposure to PFOA. However, OEHHA's rationale is not consistent with the available information on serum concentrations or PFOA production. As noted in Figure 6.2.2 of the public review draft for the proposal (page 216), and as reported in Olsen et al. (2005), PFOA serum levels were higher in 1989. The results presented in Figure 6.2.2 indicate, moreover, that serum levels may have peaked prior to the initiation of serum collection for Shearer et al. (2021). Data from the US Environmental Protection Agency (USEPA) indicate, moreover, that while production of PFOA may have peaked around 2000, production of ammonium perfluorooctanoate (AFPO) increased significantly between 1998 and 2002."

Response 7: The most thorough exposure data by year in Figure 6.2.2 in the draft PHG document comes from the Norwegian Institute of Public Health, and these data show that peak exposures occurred at about the same time that the serum samples were collected in Shearer et al. study (Shearer et al., 2021; Haug et al., 2009). The US data on serum PFOA concentrations are not as robust but track very closely with the data from Norway. High levels were seen in both the years 1990 and 2000, with lower levels before and after (references are provided in the draft PHG document). Again, these two years are at or very near the time that the serum samples were collected in Shearer et al. (2021). Overall, the available data provide good evidence that the serum samples in Shearer et al. (2021) were collected at a time when PFOA exposures were at or near their peak in most of the US population.

Olsen et al. (2005) presented serum PFOA concentrations from samples collected in the years 1974 and 1989 from volunteers living near Washington County, Maryland (Olsen et al., 2005). Because it is unknown how well this group represents the US as a whole, and because the samples were collected in only two years, this study cannot be used to estimate when peak exposures occurred. Finally, while ammonium perfluorooctanoate (APFO) production may have increased from 1998 to 2000, data from NHANES clearly show that average serum PFOA concentrations in the US declined soon after the year 2000 (Calafat et al., 2007; Kato et al., 2011).

Comment 8: "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 supplemental information provided by the authors [Shearer et al. (2021)] (https://academic.oup.com/jnci/article/113/5/580/5906528#supplementary-data) suggest that the range of serum levels was only slightly higher among the cases compared to the controls, with the exception of a 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, Shearer et al. 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. (2021) publication and would be considered "best practices" for epidemiology that is expected to become the basis for a public health regulation."

Response 8: Presumably the commenter is referring to Supplementary Figure 1 in Shearer et al. (2021) when discussing the range of PFOA values in this study. Based on this figure, the range of exposures in the cases is clearly much higher than the range in controls. While it seems likely that much of this is due to one data point, detailed information on the ranges without this outlier (or the low outlying value(s) in the controls) are not provided. Because of this, it is difficult to quantify exactly how these ranges compare without these outlying values. Regardless, it should be noted that simply

comparing ranges is generally an inexact and error-prone method for assessing causal inference.

Importantly, Shearer et al. (2021) evaluated PFOA-RCC associations using both continuous and categorical analyses. A major advantage of the latter is that they can greatly diminish the unwanted impacts of outlying values, and for this and other reasons, the results of these categorical analyses are the ones that OEHHA used to develop its PHG. It should also be noted that the results of the continuous and categorical analyses are very similar and supportive of each other, and this provides good evidence that the outlying value noted by the commenter had no major effect on continuous analysis results.

Comment 9: "Although the researchers [Shearer et al. (2021)] 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. While the number of controls selected per case may vary, it is common in the nested case-control literature to find four or five controls per case (Ernster, 1994). 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 from whom a serum sample had been collected."

Response 9: While some case-control studies have 4-5 controls per case, some have more and many have much fewer. There is no single widely accepted standard. The major reason for selecting a greater number of controls is to increase statistical power. However, the key Shearer et al. (2021) results were statistically significant. Because of this, there was little need for additional controls. Importantly, adding unnecessary control subjects would come at a cost, both in terms of time and money, and the opportunity to improve other aspects of study design (e.g., gathering better information on exposure or on confounders, increasing the number of cases, etc.).

Comment 10: "Finally, a key topic related to the variety of RCC subtypes [in Shearer et al. (2021)] that can be diagnosed is the differentiation in tumor type, by genetic basis. An analysis of the subtype of RCC has been a topic of recent interest (Wang et al., 2021) due to the variable survival rates and seemingly different course of both development and treatment. Not all RCC are the same which raises concern that any study linking PFOA to generic "RCC" could be conflating correlation with causation artificially, by not evaluating by RCC subtype. Analysis of the raw data by subtype may yield a different conclusion, and also provide clues to where to look in the animal data for subtle mode-of- action (MOA) data that could clear up the discordance between human and laboratory animal kidney disease attributed to PFOA."

Response 10: The concept that a lack of RCC subtype information "could be conflating correlation with causation" is difficult to understand. It is true that Shearer et al. (2021) only presented limited information on RCC subtypes (findings for clear cell type are provided). However, the resulting bias, if there is any, would be towards the null, not towards a false positive effect. This is because including any subtypes not caused by

PFOA would dilute, not increase, any effects seen in those subtypes that are caused by PFOA. Most likely, if the RCC subtypes that were not caused by PFOA were removed (if there are any), the odds ratios reported in Shearer et al. (2021) would be even higher.

Comment 11: "As shown in Table 2, adjusted ORs [from Vieira et al. (2013)] 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 from Comments: 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).

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

"The results from Vieira et al. (2013) summarized in Table 2 did not show statistical significance (e.g., OR with a 95%CI that did not overlap unity, or 1.0) except in the serum range considered "high" or "very high" (> 30.8 ug/L, which is several orders of magnitude higher than the proposed PHG). In addition, no evaluation of the various subtypes of RCC was conducted to try to better inform the likelihood of confounders. A detailed uncertainty analysis for assessment of the sensitivity of the decisions in study design (e.g., where to set the cutoffs for the exposure ranges) was not presented. An alternative analysis at more regular concentration/exposure ranges or with nonparametric analytical techniques may provide a different conclusion, if the raw data were to be reassessed."

Response 11: The claim that the odds ratios in the low and medium group "do not support a positive dose-response relationship for kidney cancer" does not take into account the concept of variance or the variance estimates presented in the table above. Importantly, the upper confidence intervals for these two exposure groups represent a 50 to 100% increase in risk. This claim also does not take into account the difficulties in assessing the risks at low exposures. OEHHA took all of this into account and its analyses of these data show that they are consistent with a dose-response relationship (please see the right side of Figure 6.2.4 in the PHG document as an example).

The most likely bias from a lack of subtype information would be outcome misclassification, not confounding. Please see the response to Comment 10 on this issue above.

No rationale or evidence is provided to support those contentions that "the serum concentration groupings are unevenly distributed which may impact the reported results" or that "nonparametric analytical techniques may provide a different conclusion." OEHHA evaluated these issues and saw no data or rationale to support them either.

Comment 12: "Although Vieira et al. [2013] 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. (2013) that followed the Mid-Ohio Valley residents through 2011."

Response 12: OEHHA agrees. However, because exposures were assessed using the same methods in all participants, bias from a the lack of residential history or water intake information would most likely be non-differential and therefore most likely bias results towards the null, not towards the positive effects identified. In addition, the fact that the Vieira et al. (2013) and Barry et al. (2013) results were similar provides strong evidence that the lack of residential history or water intake information was not a major source of bias in Vieira et al. (2013).

Comment 13: "The study by Barry et al. (2013) was conducted in the same study area as Vieira et al. [2013] and likely included many of the same participants. However, Barry et al. included information from additional years of follow-up and provides a more recent analysis of cancer incidence in the Mid-Ohio River Valley. Also, as indicated above and as described in more detail below, Barry et al. includes a more comprehensive assessment of exposure. Moreover, Barry et al. included an analysis of cancer incidence among the workers of the manufacturing facility whereas the previous study of these workers by Steenland and Woskie (2012) was limited to cancer mortality.

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 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.

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. Significantly, the hazard ratio is weakest for workers with a significantly higher median estimated exposure."

Response 13: The kidney cancer odds ratio in the highest exposure category of Vieira et al. (2013) was 2.0 while the corresponding odds ratio among community members in Barry et al. (2013) was 2.04. Given the similarity of these odds ratios, it is difficult to see how the association in Barry et al. (2013) could be considered "substantially reduced." With regard to workers, please see the response to Comment 11 from 3M.

Comment 14: "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."

Response 14: As outlined in the draft PHG document and responses above, OEHHA determined that the available PFOA epidemiologic studies were of sufficient quality to perform dose-response analyses and develop a PHG value. The finding of cancers in animal studies further supports the conclusion that PFOA poses a cancer risk to humans. As noted in the US EPA Guidelines for Carcinogen Risk Assessment (US EPA 2005):

> *Target organ concordance is not a prerequisite for evaluating the implications of animal study results for humans.* Target organs of carcinogenesis for agents that cause cancer in both animals and humans are most often concordant at one or more sites (Tomatis et al., 1989; Huff, 1994). However, concordance by site is not uniform. The mechanisms of control of cell growth and differentiation are concordant among species, but there are marked differences among species in the way control is managed in various tissues.

Comment 15: "The NTP bioassay reported liver adenomas and pancreatic acinar cell (PAC) adenomas in male Sprague-Dawley (SD) rats exposed to PFOA in the diet (NTP, 2019b). In the study, male rats were exposed postweaning to 0, 1.0, 2.2, and 4.6 milligrams per kilogram (mg/kg per day), while females were exposed to 0, 18.2, and 63.4 mg/kg per day. The male rat portion of the study was repeated using significantly lower exposures after 'unanticipated toxicity' was observed in male rats exposed to 150 and 300 ppm after 16 weeks. In light of the fact that male SD rats tolerated doses as high as 300 ppm in previous chronic studies (described below [Biegel et al., 2001 and Butenhoff et al., 2012]), the reports of unanticipated toxicity at comparable levels in the male rats in the NTP study raise concerns about the overall confidence in the study."

Response 15: The commenter lists two additional chronic PFOA studies, both in rats: Biegel et al. (2001) exposed male CD rats to 0 and 13.6 mg/kg-day PFOA in feed for 2 years, and Butenhoff et al. (2012) exposed male and female Sprague-Dawley rats to 0, 1.5 and 15 mg/kg-day PFOA in feed for 2 years. The high doses in these studies are comparable to the 150 ppm dose – approximately equivalent to 14.7 mg/kg-day – in the

original NTP (2020) male Sprague-Dawley rat study that was terminated early due to toxicity.

NTP performed an interim necropsy of 10 animals per dose group at the 16-week time point to evaluate a number of markers of toxicity. The concern of overt toxicity consisted of low body weights and the presence of liver necrosis. Incidences of hepatic necrosis were significantly elevated at 150 ppm (14.7 mg/kg-day) (6/10 animals) compared to control (0/10 animals) but not at 300 ppm (29.5 mg/kg-day) (2/10 animals) compared to control. Mean body weight at 14.7 mg/kg-day was approximately 78% of control. Because of the observed overt toxicity, NTP terminated the original chronic study in male rats at 21 weeks. NTP then commenced a second two-year study in male rats at a lower maximum dose of 80 ppm.

In Biegel et al. (2001), the mean body weight of male rats exposed to 13.6 mg/kg-day PFOA in feed was approximately 79% of control on day 150 of the experiment. The study did not report on liver histopathology.

In Butenhoff et al. (2012), the mean body weight of male rats exposed to 15 mg/kg-day PFOA in feed was approximately 80% of control on week 16 of the study. Incidence of hepatic necrosis (5/50 animals) was not significantly elevated relative to control (3/50 animals).

When comparing the aforementioned studies, the only difference is elevated hepatic necrosis at the low dose in the NTP (2020) study. However, this endpoint did not demonstrate a monotonic dose-response and was only significantly different from control at 150 ppm PFOA. Considering these studies were conducted years apart in different laboratories, and that animals were sourced from different vendors (Biegel et al., (2001) and Butenhoff et al. (2012) procured animals from Charles River Laboratories whereas NTP obtained animals from Harlan, Inc.), it is unlikely that sensitivity would be identical across studies.

The commenter does not provide any reasons why the results from the initial 16-week study in male rats should raise concerns regarding the overall quality of the NTP (2020) studies. The overt toxicity of concern (hepatic necrosis and reduced body weight) was lower at the 16-week interim evaluation of the second study, suggesting that the reduction in dose was appropriate. Furthermore, the NTP (2020) studies were conducted in compliance with Food and Drug Administration Good Laboratory Practices, and the protocol, analyses, and results were thoroughly audited by independent reviewers.

Comment 16: “A significant amount of genotoxicity and mechanistic data are available to assist in evaluating the results of the epidemiology and animal bioassay results described above. Multiple in vivo and in vitro assays provide clear evidence that PFOA is not mutagenic and may only cause genotoxicity at toxic concentrations.

Consequently, it is generally agreed that PFOA causes tumors in laboratory animals via a non-genotoxic or epigenetic mechanism."

Response 16: US EPA updated its PFOA assessment (US EPA, 2021a). In the new draft, the agency reports, "it is reasonable to assume that [PFOA] may act through multiple carcinogenic MOAs" and cites among other documents the genotoxicity conclusions from OEHHA's PFOA PHG draft. In its recent draft assessment, US EPA (2023) concludes that "genotoxicity cannot be ruled out as a potential MOA for PFOA-induced hepatic tumor formation."

All available mechanistic data were considered in the PHG draft. OEHHA concluded that for PFOA, multiple carcinogenic MOAs are likely, including genotoxicity.

Comment 17: "The tumor types that have been reported consistently in rats exposed to PFOA – liver, LC, and PAC – have been observed with other substances that are PPARa agonists. Because of key toxicodynamic and biological differences in responses between rodents and humans, PPARa activators are considered unlikely to induce tumors in humans. For liver tumors, this conclusion is based on minimal or no effects observed on growth pathways, hepatocellular proliferation and liver tumors in humans and/or other species (e.g., hamsters, guinea pigs and Cynomolgous monkeys) that are more appropriate animal model surrogates than mice and rats."

Response 17: Section 5.7.3 (*PPAR*α) in the draft PHG document discusses in detail all available evidence and the hypothesis of PPARα-dependent carcinogenesis of PFOA. Based on this discussion, OEHHA considers rodent liver cell, pancreatic acinar cell and Leydig cell tumors to be relevant to human health.

Comment 18: "The relevance of the liver tumor data from the animal studies is further called into question based on recent clinical data reported by Convertino et al. (2018). In a study of a sensitive subpopulation of cancer patients with normal liver function exposed to weekly PFOA doses as high as 1,200 milligrams (about 16 mg/kg per day), Convertino et al. reported no differences in clinical hepatic measures. Similarly a study of PFOA production workers reported no abnormal liver function, hypolipidemia, or cholestasis (Olsen et al., 2000)."

Response 18: The commenter has not provided any evidence that cancer patients, like the ones who participated in Convertino et al. (2018), are especially sensitive to PFOA (Convertino et al., 2018). OEHHA was unable to find any evidence for this as well. If anything, the lack of associations in Convertino et al. (2018) might actually be evidence that cancer patients are *insensitive* to PFOA. Another concern is that this study involved massive doses of PFOA, and it is unknown whether these can be used to evaluate the lower level exposures that are much more common. While Olsen et al. (2000) did not report clear and statistically significant associations between PFOA and liver toxicity or increased lipid levels in humans, a large number of larger high quality studies did. These are reviewed in Sections 5.2 and 5.3 of the draft PHG document.

Comment 19: "Several key studies provide support for the key events in the proposed PPARa-activated MOA for rat liver tumors (Table 1). These data are summarized by Klaunig et al. (2012) –

Analysis of gene expression changes elicited following short-term administration of PFOA demonstrated the up regulation of genes characteristic of PPARa activation, including genes involved in fatty acid homeostasis/peroxisomal proliferation as well as those related to cell cycle. In addition, PFOA has been shown to induce peroxisome proliferation in mouse and rat liver and causes hepatomegaly in mice and rats. While the liver growth caused by PFOA was predominantly attributed to a hypertrophic response, an increase in DNA synthesis following PFOA exposure was observed and predominated in the periportal regions of the liver lobule. Thus, the effect of PFOA on induction of cell cycle gene expression and the increase in DNA synthesis provide evidence in support of both key events 2 and 3 in the proposed MOA for liver tumor induction by PFOA. Empirical evidence also exists in support of the clonal expansion of preneoplastic hepatic lesions by PPARa activators (Step 4). Using an initiation protocol for induction of liver tumors in Wistar rats, PFOA was shown to increase the incidence of hepatocellular carcinomas in rat liver (33% in PFOA exposed rats vs. 0% in controls)."

Response 19: See Response 17 above. The PHG draft document specifically discusses the hypothesis of Klaunig and coauthors regarding the PPARα-dependent "tumor triad." It is true that PPARα can mediate liver effects in rodents and that species differences exist in PPARα activation. However, one should not exclude other MOAs simply because one MOA has been identified. Studies in PPARα knock-out mice and with constitutively active PPARα variants indicate that PFOA-induced hepatotoxicity, including carcinogenesis, in rodents is not solely the result of PPARα activation. This information with supporting references is included in Section 5.7.3 of the draft PHG document.

Comment 20: "Klaunig et al. also note that the key events in Table 4 appear in a temporal sequence and demonstrate dose-related effects further strengthening the evidence for the PPARa-agonist MOA. Although there are indications that PFOA may also act through PPARa-mechanisms independent in rodents, differences in binding affinity between the rodent and human receptors suggest that it is also unlikely that PFOA induces cancers in humans through the other mechanisms that have been suggested (Hall et al., 2012). In evaluating their results, Convertino et al. concluded that the disparity between animal and human liver endpoint studies, emphasizing a lack of risk of hepatomegaly, fatty liver, or cirrhosis, are likely due to MOA differences. Increased liver weight due to hepatocellular hypertrophy can often be an adaptive (protective) response in animals due to up-regulation of detoxification enzymes, leading toxicologists to revisit the relevance key liver endpoint studies in animals. See for example: Bjork et al. (2011)."

Table 4 from Comments: PPARa Mode of Action for PFOA-Induced Liver Tumors in Rats (Klaunig et al., 2012).

	Key Event	Support	Key Reference
1	Activation of the PPARα receptor	✓	Maloney & Waxman 1999; Vanden Heuvel *et al.* 2006
2	Induction of cell growth gene expression in the liver	✓	Martin *et al.* 2007; Kennedy *et al.* 2004
3	Cell proliferation	✓	Biegel *et al.* 2001; Martin *et al.* 2007; Thottassery *et al.* 1992
4	Selective clonal expansion of preneoplastic hepatic foci	✓	Abdellatif *et al.* 1990
5	Liver neoplasms	✓	Biegel *et al.* 2001

Response 20: See Responses 17 and 19 above.

Comment 21: "For the induction of rat PAC tumors by PFOA, the available mechanistic data are less robust, but also point to the importance of PPARa activation in the liver. Several factors may contribute to the development of PAC hypertrophy, hyperplasia, and adenomas in the rat, such as testosterone and estradiol levels, growth factor expression (cholecystokinin, or CCK), growth factor receptor overexpression (CCKA receptor), and high fat diet (Klaunig et al.). Studies with the compound Wyeth 14,643, a well-studied and potent peroxisome proliferator in rodents, suggest that peroxisome proliferation induces PAC tumors by an indirect mechanism. In this study PPARa activation in the liver caused by exposure to Wyeth triggered reduced bile flow and/or changes in bile composition that produced an increase in CCK levels secondary to hepatic cholestasis (Obourn et al., 1997). As CCK has been shown to act as a growth factor for PACs in rats, a sustained increase in CCK levels would explain the increase in PAC proliferation observed following PFOA exposure and is likely therefore a preneoplastic lesion.

Expression of CCK receptors in humans is much lower compared to rodents, and the available non-human primate and human data suggest that the CCK pathway is not relevant to human cancer risk. A study with Cynomolgus monkeys exposed to PFOA did not demonstrate an effect on CCK levels or evidence of hepatic cholestasis (Butenhoff et al., 2002). Olsen et al. (2000) reported a statistically significant negative (inverse) association between mean CCK levels and serum PFOA levels among PFOA production workers, even after adjusting for potential confounders."

Response 21: Section 5.7.3 (*PPARα*) of the draft PHG document discusses the CCK-dependent MOA of pancreatic acinar cell tumors in detail and concludes that there is little experimental support for this mechanism.

Comment 22: "OEHHA's discussion of MOA and mechanistic considerations for the carcinogenicity of PFOA is devoted almost exclusively to a discussion of effects in the liver. The discussion offers no suggestion of an MOA for kidney cancer, nor does the

document demonstrate biological plausibility for renal tumors as part of the application of the Bradford Hill criteria for causality."

Response 22: Section 5.7.3 of the draft PHG document includes discussion of available literature on tumor MOAs in Leydig cells and pancreatic acinar cells. Since renal tumors were not observed in PFOA-exposed laboratory animals, mechanistic studies in vivo, which are primarily conducted in animal models, cannot investigate the MOA.

However, in vitro evidence summarized in the framework of key characteristics of carcinogens applies to many organ sites including the kidney. Based on available evidence, a genotoxic MOA for PFOA carcinogenesis cannot be ruled out, and therefore, tumor site concordance would not be required to establish biological plausibility. Genotoxic carcinogens can potentially cause DNA damage in any organ.

Comment 23: "The failure to offer evidence for an MOA is particularly concerning given OEHHA's use of peak exposure as a more relevant exposure metric than cumulative exposure approach used by both Vieira et al. and Barry et al. The decision appears based more on justifying the use of the Shearer et al. data, and rejecting the data from Barry et al., than on any biological or mechanistic rationale.

As noted above the time period in which the serum samples were collected in the population studied by Shearer et al. and Vieira et al. does not represent peak exposure as USEPA data indicate that production and import of PFOA and its ammonium salt continued to increase during this period. Moreover, OEHHA has not offered any possible explanation for why peak exposure is more relevant and, in fact, reasons elsewhere in the draft PHG document that "a single measurement of PFOA or PFOS can be a good long-term marker of exposure in many people." The analysis conducted by Vieira et al., summarized in Table 2, shows little difference between the odds ratios calculated using "peak" and cumulative exposure."

Response 23: Please see the response to Comment 7 about the peak exposure period. The comment contains no evidence that cumulative exposure is a better metric for assessing PFOA risks than peak exposure, and OEHHA was unable to find any either. The long half-life of serum PFOA and the fact that risks are similar for peak and cumulative exposure both provide evidence or justification that peak exposure is an accurate metric for assessing the true cancer risks of PFOA.

Comment 24: "Contrary to OEHHA's analysis, both the European Food Safety Authority (EFSA, 2020) and Canada Health (Health Canada, 2018) have concluded that the available evidence does not support the carcinogenicity of PFOS. The EFSA and Health Canada conclusions are based on a thorough review of the human and animal data for the substance."

Response 24: In identifying the toxicological hazards of PFOS, EFSA (2020) primarily relied on the previous assessment by the Contaminants in the Food Chain (CONTAM)

panel, which concluded that “PFOS was found to be tumorigenic in the liver” and “the liver is the main target organ for chronic toxicity and carcinogenicity of PFOS” (EFSA, 2018).

In contrast to what the commenter states, Health Canada (2018) referred to “carcinogenic effects of PFOS” and developed a cancer total daily intake (TDI) based on hepatocellular tumors in male rats (Butenhoff et al., 2012a), based on the same critical study used by OEHHA for the draft PHG.

Comment 25: “Several epidemiology studies have attempted to assess cancer incidence in populations exposed to PFOS, including both occupational and community studies. The worker studies have focused on a fluorochemicals production facility in Alabama. Significant community studies include populations in France, Denmark, Sweden, Holland, Taiwan, and Greenland. These studies show no association of PFOS with liver, pancreatic, or prostate cancer or of cancers of the digestive, respiratory, lymphatic, or hematopoietic systems. While Alexander et al. (2003) reported an increase in in [sic] bladder cancer in the worker population in Alabama, a more detailed follow-up study found no association with bladder cancer and PFOS exposure (Alexander and Olsen, 2007). No increase in breast cancer incidence was observed among 263 female employees at the production facility in Alabama, although the number of cases was too small for further analysis (Grice et al., 2007).”

Response 25: OEHHA agrees that the human epidemiologic evidence linking PFOS to cancer is not as strong as that for PFOA. For this reason, OEHHA has chosen to use results from animal studies for the proposed PFOS PHG.

Comment 26: “Several community studies have investigated the association with breast cancer and have reported mixed results. In general, the number of cases investigated in these studies has been relatively small – significantly limiting their interpretation. Two recent case-control studies have investigated the hormone receptor status among women with breast cancer in France and Taiwan. Both have suggested an association between PFOS exposure and estrogen receptor positive (ER+) tumors, the most diagnosed tumor type. In both studies, the analysis was based on a single blood sample which, in the case of the study of French women was collected several years before cancer diagnosis. PFOS levels vary widely between the two studies, with the blood collected in the Taiwan study between 2013 and 2015 – well after the voluntary phase out of PFOS in Japan, Europe, and the US. As a result, the relevance of the PFOS blood levels is uncertain.

Mancini et al. (2020) investigated breast cancer incidence in 194 post-menopausal women (mean age of diagnosis – 68.8, range 58.3 to 84.9) diagnosed prior to 2013 for which a single blood sample had been collected between 1994 and 1999. No summary data on PFOS levels is provided, but levels ranged from 5.8 to 13.6 nanograms per milliliter (ng/mL) in the lowest quartile of serum level to 22.5 to 85.3 ng/mL in the highest quartile. Mancini et al. report no association with breast cancer incidence in their adjusted model including eight covariables (Model 1), and an association for quartiles 2

and/or 3 but not quartile 4 in the unadjusted and two other adjusted models (Models 2 and 3). In all, 15 covariables were included in Model 3. The association with ER+ tumors was only observed in adjusted Model 3 where the inclusion of so many covariables results in wide confidence intervals, limiting the study's power.

In a study of Taiwanese women, Tsai et al. (2020) observed an association between PFOS levels and the incidence of breast cancer overall and for ER+ tumors in 120 woman less than 50 years old (mean age of 48.9 at diagnosis). The mean serum level in the women was 5.64 ng/mL, which represents the lowest serum level quartile in the study by Mancini et al. Contrary to the results of the Mancini study, there was no association with breast cancer or ER+ tumors in woman over the age of 50 – despite the fact these women were likely to have experienced higher overall exposure to PFOS. Interpretation of these results is complicated by an overall increase in breast cancer incidence among younger women in Taiwan and other East Asian countries which has been associated with a reduction in the number of births and an increase in the child bearing age of the women (Chen et al., 2018). The study also may be complicated by exposure to other pollutants."

Response 26: OEHHA did not use the studies cited by the commenter, or any other human epidemiologic study, as the basis for its PFOS PHG.

Comment 27: "Only one chronic animal bioassay [Butenhoff et al., 2012] has been performed for PFOS." "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 CAR/PXR activation [Elcombe et al., 2012a], suggests that the liver tumors observed in the rats may be of limited relevance to humans. The authors concluded that the liver effects were consistent with PPARα and CAR/PXR activation and that the available human and animal data 'do not provide support for cancer risk from exposure to PFOS.'"

Response 27: The PHG draft document provides a very detailed MOA analysis for PFOS carcinogenesis in section 5.7.3. All available evidence for non-genotoxic and receptor activated mechanisms (alternative MOAs that the commenter refers to) is considered. Based on the available evidence, OEHHA concluded that PFOS should be evaluated as a carcinogen. This is supported by the decision of California's Carcinogen Identification Committee to list PFOS as a carcinogen under Proposition 65. The authors of any particular study may reach their own conclusions based on their own experimental data, institutional bias (both cited studies are affiliated with a PFOS manufacturer) and literature available at the time.

Comment 28: "Supporting documentation developed by OEHHA also reviews the findings of mechanistic studies examining the effects of PFOS on seven characteristics that have been identified as associated with carcinogenicity (Smith et al., 2016). Although the application of these characteristics may be useful for identifying and organizing relevant data, it is critical that they be combined with an understanding of the plausibility and causal linkages of the sequence of key events and biological responses

involved in carcinogenesis (Becker et al., 2017a). Without a critical evaluation and integration of the mechanistic evidence with the other realms of evidence, moreover, application of the identified characteristics is of limited value in supporting a scientifically defensible conclusion of carcinogenicity (Goodman and Lynch, 2017).

The limitations of the key-characteristics approach have been highlighted by two recent publications. The first by Bus (2017) reviews the challenges in the use of oxidative stress as a key characteristic in the evaluation of glyphosate by the International Agency for Research on Cancer (IARC). The second publication by Becker et al. (2017a) applied the key characteristics to the data from high-throughput studies for about 250 chemicals evaluated for carcinogenicity by USEPA's Office of Pesticide Programs for which ToxCast/Tox21 data are available. The authors conclude that the ability to predict cancer hazard by applying the key characteristics, alone or in combination, with the high-throughput data was "no better than chance." Moreover, interpretation of in vitro assays is complicated by the surfactant properties of PFOS and other PFAS (Chiu et al., 2018)."

Response 28: The comment suggests that "applying the key characteristics of carcinogens alone or in combination with the high-throughput data" is unreliable in predicting cancer hazard. The PHG draft document did not use such an approach. Rather, critical evaluation and integration of the mechanistic evidence (Section 5.7.3 and Appendix 8) provided support to the animal bioassay findings, allowing OEHHA to reach the overall conclusion to analyze PFOS as a carcinogen. This approach is consistent with the general recommendations cited in the comment (Becker et al., 2017b; Goodman and Lynch, 2017).

Comment 29: "Internal dose ratios predicted by the available physiologically-based pharmacokinetic (PBPK) models indicate, however, that the interspecies extrapolations for PFOA and PFOS are highly dose dependent, and result from nonlinear toxicokinetics (Loccisano et al., 2012). As a result, a single interspecies extrapolation factor such as that used by OEHHA is not scientifically supportable for either PFOA or PFOS. Instead, an approach that uses CSAF values derived from the PBPK models better addresses the issue of nonlinear toxicokinetics and its impact on interspecies extrapolation."

Response 29: Different toxicokinetic approaches to interspecies extrapolation have distinct advantages and disadvantages. As detailed in the draft PHG document, OEHHA considered PBPK models for PFOA and PFOS and found them lacking in certain aspects that would lead to increased uncertainty if used. It is not reasonable to argue that just because a chosen approach has limitations, a different, much more uncertain approach (such as a PBPK-centered method) should be used instead.

It is correct that PFOA and PFOS toxicokinetics in experimental animals is non-linear, and that a single extrapolation factor cannot be used to correlate serum concentrations and administered dose over a wide range of doses. However, this is the exact reason OEHHA did not consider PFOA or PFOS animal studies that only report administered

doses in HPC derivation. Instead, only studies that reported serum concentrations in experimental animals were considered. This allowed OEHHA to avoid the toxicokinetic challenge of non-linear extrapolation without the need to resort to PBPK models that can introduce additional uncertainty.

In the PHG draft document, OEHHA did not use "an interspecies extrapolation factor" but rather a human clearance factor that allows predictions of administered dose from serum concentration. This approach is commonly used in the PFOA and PFOS regulatory literature. Due to very slow elimination, the toxicokinetic behavior of either PFAS is readily extrapolated by a first-order elimination single compartment model, which is the theoretical basis for using a clearance factor in estimating administered doses.

Comment 30: "Using such an approach, Health Canada compared dose metrics predicted by the various PBPK models to calculate a CL ratio between species (CL_A/CL_H) (Health Canada, 2018). They reasoned that using the model data to derive the CL_A/CL_H allows for a more appropriate comparison of doses of the same magnitude. Using the CL ratio to estimate exposures, Health Canada's analysis indicates that the approach taken by OEHHA significantly underestimates the human clearance rate and, as a result, OEHHA calculates HED values that are 10 to 500 times lower than actual. The decline in biomonitoring data by the Center for Disease Control and Prevention (CDC) over the last 20 years support this point (https://www.cdc.gov/exposurereport/index.html)."

Response 30: It is not clear what the commenter means by "They reasoned that using the model data to derive the CL_A/CL_H allows for a more appropriate comparison of doses of the same magnitude." Presumably, the commenter is referring to the need to use PBPK models on the animal side of the species extrapolation, an issue that does not apply to OEHHA's toxicokinetic adjustments in the PHG calculation (see Response 29 above). Moreover, neither the PHG draft document nor the Health Canada (2018) assessment used human PBPK models in their toxicokinetic adjustments. Health Canada (2018) specifically indicated that "the human PBPK models that would be used to extrapolate from this serum concentration cannot be fully verified based on existing human pharmacokinetic data, which decreases the level of comfort of using this approach to estimate precise PODs." This is similar to OEHHA's conclusions.

To calculate human clearance (hCL) for PFOS, Health Canada (2018) used its estimated half-life and volume a distribution, a method which OEHHA considered and analyzed in great detail in the PHG draft document. The calculated hCL was 0.07 ml/kg-day, which is 5.5 times lower than the value chosen by OEHHA (3.9×10^{-4} L/kg-day). Thus, the Health Canada (2018) value is more conservative than that of OEHHA, and would result in lower HEDs if compared side-by-side to OEHHA calculations. This is the opposite of what the commenter states. The difference in the Health Canada hCL compared with OEHHA's clearance value is due to longer half-life and smaller volume of distribution estimates that were chosen for the hCL prior to the availability of the more

recent literature used by OEHHA. OEHHA also provides a thorough review not only for this but also for all other available methods.

As detailed in the PHG draft, half-life estimates based on the type of disappearance trend that can be derived from the biomonitoring data over the last several decades provide higher PFOA and PFOS half-life estimates (see Tables 4.7.1 and 4.7.2 in the PHG draft document) presumably due to the lack of or difficulty in estimating ongoing background exposures. Using such higher half-life estimates would also result in lower hCL values and more conservative HEDs, which is the opposite of what the comment suggests.

Comment 31: "As described, the risk assessment calculations by OEHHA are highly dependent on the estimate of the elimination half-life in humans. Reported half-life estimates in humans range considerably and appear to show a gender difference for at least some PFAS. Estimates of the mean half-life for PFOA vary from 2.3 years in a study of a general population exposed via drinking water (Bartell et al., 2010) to 3.8 years in an occupationally-exposed cohort (Olsen et al., 2007). For PFOS, a recent analysis of data from the CDC biomonitoring data estimated a serum elimination half-life of PFOS of 3.8 years in males and 3.4 years in females (Gomis et al., 2017). Similarly, data from a community in Sweden exposed to PFAS via a contaminated water supply following installation of a treatment system suggested a serum elimination half-life for PFOS of 3.4 years for 106 residents aged 4 to 83 (Li et al., 2018). An earlier study of occupational exposures, on the other hand, suggested a half-life of 5.4 years for PFOS among retired workers."

Response 31: OEHHA acknowledges the comment. The PHG draft document summarizes and analyzes all available half-life estimates for PFOA and PFOS, even though the half-life-based calculation was not the chosen as the toxicokinetic adjustment method for developing the HPCs.

Comment 32: "In both cases, a benchmark response (BMR) of 5 percent 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 (OEHHA, 2009). 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."

Response 32: OEHHA's guidance on BMR selection when evaluating dichotomous data is described in OEHHA (2008), *Technical Support Document for the Development of Noncancer Reference Exposure Levels*. The guidance went through public comment as well as scientific peer-review by the State's Scientific Review Panel on Toxic Air

Contaminants (SRP),[6] and is consistent with the US EPA guidelines (US EPA, 2012). As noted in these peer-reviewed risk assessment guidelines (OEHHA, 2008),

> "[Reference concentration] determinations for various endpoints by the U.S. EPA have used either 5% or 10% as the benchmark response rate, depending on the statistical uncertainty in the data (U.S. EPA, 2002a; U.S. EPA, 2004). OEHHA has used the 5% response rate in several chronic [reference exposure levels], and showed that the lower 95% confidence bound on the BMC_{05} [benchmark concentration for a BMR of 5%] typically appears equivalent for risk assessment purposes to a NOAEL in well designed and conducted animal studies where a quantal measure of toxic response is reported…Therefore, OEHHA typically uses a 5% response rate as the default for determination of the BMC from quantal data (i.e. the effect is either present or it is not) in animals."

While the US EPA in its *Benchmark Dose Technical Guidance* (US EPA, 2012) notes, "For comparing potencies across chemicals or endpoints (e.g., for chemical rankings) for dichotomous data, a response level of 10% extra risk has been commonly used to define BMDs, also known as effective doses (i.e., ED_{10}s)," the guidelines also state, "[T]he BMD (BMDL) used as a POD may correspond to response levels below (or sometimes above) 10% extra risk. For standardization, rounded levels of 1%, 5%, or 10% have typically been used."

Comment 33: "OEHHA also applied a body weight scaling factor to the human equivalent dose (HED) for PFOS (According to the draft PHG, OEHHA applied an adjustment of $(BW_{animal}/BW_{human})^{1/8}$ to account for toxicodynamic differences between the species), despite using a benchmark dose (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

[6] Approved by California's Scientific Review Panel on Toxic Air Contaminants June 18, 2008.

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. (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."

Response 33: In cancer slope factor derivation, OEHHA typically applies low-dose linear extrapolation. However, the resulting cancer slope factor is adjusted by $(BW_{animal}/BW_{human})^{1/4}$ to account for interspecies differences. Without such adjustment, it would be implied that doses applied to animals would be equipotent in humans, which is incorrect. Since the use of animal serum concentrations (and not administered doses) would account for the toxicokinetic interspecies differences, the interspecies adjustment factor was reduced from $(BW_{animal}/BW_{human})^{1/4}$ to $(BW_{animal}/BW_{human})^{1/8}$ to adjust for remaining possible toxicodynamic differences.

Comment 34: "We also are concerned about the use of a relative source contribution of 20 percent to develop the draft non-cancer PHGs for PFOA and PFOS. Although 20 percent is often used as a default assumption for the exposure resulting from drinking water, the available evidence suggest that other sources of potential exposure to PFOA and PFOS have declined drastically. According to data collected by the Center for Disease Control and Prevention (CDC), mean serum levels of PFOS declined by 85 percent in the US population between 1999 and 2016 (https://www.cdc.gov/exposurereport/index.html). According to CDC, mean serum levels of PFOA declined by 60 percent over the same time frame (see Figure 1). Given those dramatic declines, it is inappropriate to assume that 80 percent of exposure to these substances comes from sources other than drinking water. While a few other states have assumed an RSC of 50 or 60 percent, it is likely that the contribution of drinking water to overall exposure is even higher – particularly in areas where drinking water contamination has been detected."

Response 34: While gradual decreases of PFOA and PFOS in serum are documented (see Table A5.2 in the PHG draft document), there is no reason to believe that exposure to PFOA and PFOS from water remains elevated while other routes of exposure are decreasing. The comment does not provide any scientific references to support this opinion. Direct estimates of PFOA and PFOS also generally produced an RSC of 20% or lower (see Table A5.2 in the PHG draft document). Different regulatory assessments may have different RSC estimates depending on a multitude of factors. RSC can be specific to a life-stage or the exposure scenario for the most sensitive group. The recently released US EPA draft of proposed approaches for deriving Maximum

Contaminant Level Goals for PFOA and PFOS in drinking water identified 20% RSC as appropriate for either compound.[7]

[7] The draft documents are available at: https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601

CALIFORNIA ASSOCIATION OF MUTUAL WATER COMPANIES

Comment 1: "The substance of CalMutuals' comments addresses the regulatory framework that will lead to development of the final PHG for PFOS and PFOA. The current regulatory environment leading to OEHHA's proposed PHG is presenting unique challenges to our members given that the final PHG will likely be treated as enforceable standards by some agencies of the state. OEHHA's traditional responsibility is to set PHGs using the most current scientific research and data, without consideration of other limiting factors such as cost. In so doing, OEHHA is supposed to allow only for consideration of technical research with the aim of setting a PHG reflective of the best available technologies. In normal circumstances the State Water Resources Control Board would follow the adopted PHG to set a maximum contaminant level (MCL), which would be the enforceable standard, as close to the final OEHHA PHG as possible.

… the regulatory framework under which the PHG and RL for PFAS chemicals are being developed may create trade-offs leading to adverse health effects in DAC/SDAC communities, as well as public distrust in local water systems. This is why the net impact to public health caused by the proposed PHG should not be summarily dismissed.

While a final PHG may justifiably indicate a reduction of cancer risk from PFOS and PFOA, given the regulatory framework in play, other health risks may transpose themselves. For example, numerous studies by the Natural Resources Defense Council indicate that people of color and low-income communities already distrust tap water for drinking, preferring lesser regulated bottled water or vending machine sources. The regulatory confusion where some communities can afford to react to non-enforceable standards for PFOA and PFOS with treatment that others cannot afford threatens to confirm distrust of public water systems. As a result of the reliance on bottled and vending machine drinking water, according to NRDC, such populations suffer from disproportionate rates of dental decay and gastrointestinal ailments.

… We believe that the health impacts should be properly calibrated to prevent trade-offs created by flawed regulatory framework that works against itself. Such a regulatory framework perpetuates social inequality as it pushes disadvantaged communities to make decisions that may impact public health out of fear, not science."

Response 1: OEHHA acknowledges the comment. As the comment correctly notes, PHGs are not legally enforceable standards, and are based solely on public health considerations. The PHG does not reflect the current technologies or treatment methods, but represents a goal the State Water Resources Control Board and water systems should strive to achieve if feasible. OEHHA defers on all issues related to setting MCLs, RLs and PFAS-related water policy to the Water Board. The basis for the statement that the final PHG will likely be treated as enforceable standards by some agencies of the state is unclear. There are a number of MCLs set at different levels than their respective PHGs and this does not appear to be the case in those circumstances. The Water Board sets drinking water standards based on the PHG, but also considers

economic and technical feasibility. OEHHA understands that MCLs set by the Water Board may affect communities differently, but an analysis of the social impacts and behaviors attributed to water policy is beyond the scope of this document.

CALIFORNIA ASSOCIATION OF SANITATION AGENCIES

Comment 1: "The PHGs should be based on experimental animal data.

Epidemiological studies can provide supporting evidence regarding potential human health effects from chemical exposures. However, human data are often inadequate for direct quantitative use in risk assessment and/or establishing public health goals due to significant uncertainty and challenges associated with confounding, sample size, and exposure assessment. As such, human data are generally useful only as a qualitative line of evidence, when observations demonstrate consistency with animal data and biological plausibility for human relevance. In the case of PFOA, the available epidemiology data do not corroborate the animal studies and are fraught with uncertainties and limitations. Therefore, the PFOA PHG should be based on experimental animal data with observations that provide a clear dose- response and human relevant biologically-plausible endpoint."

Response 1: OEHHA agrees that there are instances where human data are inadequate for establishing HPCs and PHGs, but that was not the case for PFOA. As documented in the *Dose-Response Assessment* chapter of the draft PHG document, several high quality human studies were available for assessing dose-response for both the cancer risks and non-cancer health effects of PFOA.

Comment 2: "The weight of evidence for cancer effects for PFOS indicates the compound is unlikely to present a carcinogenic risk, especially at low levels. In addition, OEHHA misapplied IARC's key characteristics of carcinogens for PFOA and PFOS. Therefore, the PHGs should be based on noncancer health effects."

Response 2: OEHHA's conclusion, given all the available data, is that PFOS should be evaluated as carcinogen. Mechanistic studies of PFOS have shown that it possesses several of the key characteristics (KCs) of carcinogens, including the ability to induce oxidative stress, inflammation, and modulate receptor-mediated effects. KCs of carcinogens were used to identify and organize data relevant to carcinogenicity, so it is unclear exactly how these data were "misapplied." As discussed below (see response to Comment 5), IARC classified PFOS as a Group 2B carcinogen based on strong evidence for two key characteristics. These data together with the animal evidence support OEHHA's decision to treat PFOS as a possible carcinogenic hazard. Furthermore, PFOS was designated as a carcinogen under Proposition 65 by the State's Carcinogen Identification Committee, a committee of experts from the State's academic institutions and business.

Comment 3: "The available PFOS laboratory animal and epidemiology data evaluating cancer risk is largely negative, with no clear association between exposure and increased cancer risk noted, therefore, the Butenhoff et al. (2012a) animal study should not be used to support an OEHHA PHG.

The animal data evaluating PFOS carcinogenicity are "suggestive", not definitive, based on the available data (only one chronic animal bioassay) and numerous authoritative agency reviews (e.g., USEPA, European Food Safety Authority, Health Canada). OEHHA's evaluation contradicts these other recent authoritative and comprehensive reviews. The rodent liver tumors from Butenhoff et al. (2012a) are of questionable human relevance due to potential species-specific mode of action considerations (non-human relevant mechanisms involving xenobiotic nuclear receptors, such as peroxisome proliferator activated receptor-alpha (PPARa)) (Elcombe et al., 2012a). Furthermore, the liver tumors noted with statistical significance were actually benign adenomas; no statistically significant increases in hepatocellular carcinomas were observed in either the male or female rats and no clear dose response was noted. These data are not strong enough to suggest that PFOS is carcinogenic to humans at low doses, and no other data provide PFOS carcinogenicity evidence in animal bioassays.

Epidemiology studies have not reported a consistent or clear increase in cancers for occupational workers, impacted communities, or general population cohorts exposed to PFOS..."

Response 3: As the comment correctly notes, many epidemiological studies of PFOS carcinogenesis had significant limitations that may explain the lack of association between PFOS exposure and outcomes. While only one cancer bioassay reported carcinogenesis due to PFOS exposure (Butenhoff et al., 2012a), tumors were observed in both sexes and multiple organs. Based on these data and analysis of mechanistic studies, OEHHA concluded that PFOS should be evaluated as a carcinogen. The comment does not provide new information that can change this conclusion.

The US EPA Scientific Advisory Board (2019) in their review stated the following regarding the Butenhoff study:

> "[T]he interpretation of the hepatocellular carcinoma data from the Butenhoff (2012) study in the 2016 HESD is overly conservative in dismissing the appearance of a dose-response relationship for this endpoint, particularly in females. Relevant to this point, it is noted that DWQI (2018) developed a CSF based on the incidence of hepatocellular tumors in females in Butenhoff et al. (2012). Given that multiple MOAs may be operative in this outcome, the Panel suggests that the EPA reevaluate the 2012 Butenhoff study."

More recently, US EPA (2023) stated:

> "EPA has now determined the available data for PFOS surpass many of the descriptions for *Suggestive Evidence of Carcinogenic Potential* according to the *Guidelines for Carcinogenic Risk Assessment."*

EFSA acknowledged and did not dismiss the cancer findings in Butenhoff et al. (2012a) although it relied on human studies reporting immunotoxicity for its dose-response

assessment (EFSA, 2018, 2020). Health Canada developed a cancer-based reference dose based on the Butenhoff et al. study (Health Canada, 2018).

US EPA and EFSA do not dismiss the cancer findings in Butenhoff et al. (2012a). Their dose-response assessment is based on other studies, e.g., for preference for human data in choosing critical effects (EFSA, 2018, EPA, 2021).

The draft PHG reviewed the PPARα-dependent cancer MOA for PFOA and PFOS in detail in section 5.7.3 and concluded that other MOAs cannot be excluded.

Regarding the tumor types, for cancer dose-response analysis, adenomas and carcinomas in the liver can be combined since (i) progression of adenomas to carcinomas is expected and (ii) cross-sections of liver tumors may not always detect malignant sites (McConnell et al., 1986).

Comment 4: "OEHHA's conclusion that PFOA and PFOS are genotoxic conflicts with conclusions by numerous state, federal, and international organizations. Genotoxicity is not a mode of action relevant for PFOA or PFOS and should not be used as a supporting line of evidence for PHGs based on cancer."

OEHHA's representation of the weight-of-evidence of PFOA genotoxicity contradicts recent conclusions by Minnesota, New Jersey, and the International Agency for Research on Cancer (IARC). In their recent derivations of health-based drinking water values, both Minnesota and New Jersey clearly state PFOA is unlikely to be genotoxic.

In Section 6.2.2 of the PHG document, OEHHA states '*There is evidence to indicate that PFOS is genotoxic*'. This statement is inconsistent with conclusions made by New Jersey, USEPA, and the Agency for Toxic Substances and Disease Registry (ATSDR) on PFOS genotoxicity. USEPA has also reached similar conclusions on PFOS genotoxicity (US EPA, 2016b).

OEHHA appears to rationalize the contradiction between their findings on the genotoxicity of PFOS and the conclusions of numerous state, federal, and international agencies by suggesting that OEHHA identified four additional genotoxicity studies that were not reviewed by other agencies. However, a recent European Food Safety Authority (EFSA) publication reviewed three of the additional genotoxicity publications noted by OEHHA, and still concluded '*For PFOS and PFOA, no evidence for a direct genotoxic mode of action was identified*' (EFSA, 2020). The fourth study is a PFOS biochemical study with no direct relevance to evaluation of genotoxicity."

Response 4: OEHHA has reviewed the work of these other agencies and is aware of different conclusions regarding the genotoxicity of PFOA and PFOS. OEHHA independently analyzed all available genotoxicity studies. As detailed in sections 5.7.3 and 5.7.4, and Appendix 8 of the draft PHG document, several studies, including those in animals, provide evidence of mutagenesis, chromosomal effects and DNA damage. Other studies found no evidence of genotoxicity. OEHHA qualified the overall

genotoxicity evidence for PFOA and PFOS as suggestive and concluded that a genotoxic MOA for cannot be dismissed. This conclusion is based on the overall body of evidence and not on combining the EFSA (2020) determination with the "four additional genotoxicity studies."

Furthermore, some agencies cited in the comment did not dismiss genotoxicity outright.. For example, EFSA (2018) states:

> "From *in vitro* and *in vivo* genotoxicity studies, there is no evidence for a direct genotoxic mode of action for both PFOS and PFOA, however, **genotoxicity cannot be excluded** [emphasis added]. There is some evidence for oxidative stress induced by both PFOA and PFOS."

EFSA (2020) indicated that their conclusions did not change from those in 2018.

While PFOA and PFOS were negative in many direct genotoxicity assays, several in vivo studies provided evidence that these chemicals are genotoxic in vivo, supporting OEHHA's conclusion that "a genotoxic MOA for cancer cannot be dismissed." All studies are listed in Appendix 8. The same distinction applies to several other quotes cited in the comment. Furthermore, although direct mutagenic evidence is lacking for PFOS, there are a number of positive key characteristics of carcinogens for both PFOA and PFOS and absent any known carcinogenic MOAs, OEHHA evaluated PFOS using its default methodology.

Comment 5: "OEHHA misapplied IARC's key characteristics of carcinogens; the key characteristics of carcinogens should not be used as supporting evidence for cancer-based PHGs. Ten key characteristics of carcinogens (KCs) were described by the IARC Working Group as characteristics exhibited by known human carcinogens (Smith et al., 2016). However, it is important to note that the IARC working group did not evaluate incidences of KCs for chemicals that did not cause cancer, and did not quantitatively evaluate the association between the dose-response of a specific carcinogenic effect and the KCs (Doe et al., 2019). KCs are highly qualitative and are ineffective at utilizing available data for causal analysis (Becker et al., 2017b). In large datasets on specific KCs or proposed mechanisms of action such as genotoxicity, it is not uncommon to have some positive results despite an overwhelming majority of negative findings ((Becker et al., 2017b).

While KCs may occur in the formation of tumors, they only serve as one line of evidence for carcinogenicity. Their occurrence alone should not inherently result in the classification of the chemical as a carcinogen (Doe et al., 2019). Additional considerations should include quantitative dose and temporal evaluations of the chemical- and tumor-specific sequences of molecular events leading to tumor development against a human relevance framework.

KCs were used by OEHHA in the draft PFOA and PFOS PHG document to identify and discuss plausible mechanisms of carcinogenesis, and at least in part, to justify linear

extrapolation in the derivation of the cancer slope factors. OEHHA determined both PFOA and PFOS had relevant data for five of the ten KCs. However, OEHHA did not apply any quantitative scoring method to evaluate confidence in these characteristics and failed to take into account the well-established understanding of cancer etiology and progression along a dose- and time-response continuum."

Response 5: Becker et al. (2017) utilized data from ToxCast alone, which were not designed to query for KC activity, and provide very limited information on whether key characteristics are present.

Evidence on Key Characteristics is used by the International Agency for Research on Cancer (IARC) in classifying agents in terms of their carcinogenic potential. For example, as outlined in the IARC (2019) Preamble:[8]

> The Category "Group 1" – "is carcinogenic to humans" – "may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals."
>
> The category "Group 2B" – "possibly carcinogenic to humans" – "generally applies when only one of the following evaluations has been made by the Working Group:
> - *Limited evidence of carcinogenicity* in humans
> - *Sufficient evidence of carcinogenicity* in experimental animals
> - *Strong evidence that the agent exhibits key characteristics of carcinogens*."

Most recently, IARC (Zahm et al., 2023) utilized the key characteristics in evaluating the carcinogenic hazard of PFOA and PFOS. IARC concluded that:

> "The mechanistic evidence was 'strong' in exposed humans because PFOA was found to induce epigenetic alterations and to be immunosuppressive," which are two KCs.

Consistent with the IARC Preamble,

> "PFOA was classified as 'carcinogenic to humans' (Group 1) based on 'sufficient' evidence for cancer in experimental animals and 'strong' mechanistic evidence in exposed humans."

IARC (Zahm et al. 2023) further concluded,

> "Similarly to PFOA, PFOS induces epigenetic alterations and is immunosuppressive in exposed humans. The evidence for PFOS is corroborated

[8] Available online at: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf

> by consistent and coherent findings both in human primary cells and experimental systems. PFOS equally induces oxidative stress in human primary cells and experimental systems. Notably, PFOS also modulates thyroid-mediated and androgen-mediated effects in experimental systems, and PPARα and CAR/PXR in both human primary cells and experimental systems. Metabolomic and transcriptomic data support the mechanistic evidence."

Based on the evidence on these key characteristics, IARC identified PFOS as a Group 2B carcinogen: possibly carcinogenic to humans.

Thus, evidence on the key characteristics of carcinogens is part of the IARC framework for classifying carcinogens, in addition to being used to organize mechanistic evidence in support of the cancer studies.

Key events of cancer MOAs, their progression and dose-response are discussed in Section 5.7.3.

Comment 6: "OEHHA's use of epidemiological data to derive the PFOA cancer slope factor is highly uncertain.

Translating two epidemiological studies - Shearer et al. (2021) and Vieira et al. (2013) - into a PFOA cancer slope factor is a relatively complex, yet consequential step in the derivation of the PFOA PHG. While there is precedent for using epidemiological studies in the derivation of cancer slope factors (OEHHA, 2004; US EPA, 2011), OEHHA does not appropriately contextualize shortcomings in the use of Shearer et al. (2021) for the derivation of the PFOA cancer slope factor and subsequent draft PHG. Additionally, the statistical values selected by OEHHA from Shearer et al. (2021) for derivation of a cancer slope factor are inconsistent with best practices for human health risk assessment.

Shearer et al. (2021) categorized PFOA serum concentrations into quartiles, then utilized the lowest quartile (<4 ng/ml) as the reference group to derive PFOA serum concentrations and renal cell carcinoma (RCC) odds ratios (ORs). Importantly, Shearer et al. (2021) estimated exposure to PFOA and other PFAS from a single blood sample. As summarized by Steenland and Winquist (2021), while PFAS serum levels can serve as useful biomarkers of exposure, PFAS serum levels collected at a single timepoint may not accurately represent historical exposure. Therefore, the single blood sample values in Shearer et al. (2021) should be treated with a low degree of confidence when used to represent lifetime PFAS exposure.

Shearer et al. (2021) identified ORs for PFOA serum concentrations and RCC that were corrected for numerous confounders, including age, sex, study center, race, blood sample year, BMI, smoking habits, EGFR, freeze-thaw cycles, and hypertension history. Only the OR for the highest quartile was statistically significant for PFOA. However, once the authors adjusted the PFOA concentrations and RCC ORs for co-exposure to PFOS and PFHxS, no OR remained statistically significant, only the continuous variable

for PFAS adjusted ORs was significant. Nevertheless, OEHHA elected to use the unadjusted ORs for the calculation of the PFOA cancer slope factor instead of the ORs that were adjusted for co-exposure to other PFAS. This is a scientifically unjustified approach.

The use of Shearer et al. (2021) to quantify PFOA's PHG is highly uncertain. OEHHA should consider the fact that Shearer et al. (2021) is inadequate for quantitative assessment of human health cancer risk based on an estimate of exposure from a single blood sample and the lack of quartile statistical significance once ORs were adjusted for co-exposure."

Response 6: The commenter seems to be suggesting that the use of a single serum sample to assess PFOA exposure is likely to be associated with significant bias, although no evidence for this is presented. Because of the long half-life of PFOA in serum, a single measurement likely represents long-term exposure in most people. And because PFOA was measured using the same methods in both cases and controls, bias due to errors in exposure assessment will most likely be towards the null, not towards the positive effects identified. Even in the remote possibility that the bias would be away from the null, the notion that it could be strong enough to cause an odds ratio as high as 2.63, as reported in Shearer et al. (2021), is implausible (Shearer et al., 2021).

Comment 7: "The weight of evidence better supports use of noncancer data for both PFOA and PFOS PHGs, however, the draft noncancer PHGs should be revised.

The immunotoxicity database shows inconsistent associations between PFOA and PFOS and immune endpoints, including largely negative associations with actual infections or symptoms, such that an additional uncertainty factor to cover immune databases is unnecessary.

OEHHA applied an uncertainty factor (UF) for intraspecies variation of three to the point of departure (POD) for noncancer effects to calculate the acceptable daily dose (ADD) for both PFOA and PFOS. For PFOA, OEHHA indicated that the UF is justified, in part, by the 'strong evidence for immunotoxicity of PFOA', and 'the potential for immunotoxicity to occur below the [no-observed-adverse-effect concentration] for elevated [alanine aminotransferase] levels'. Given the large number of studies that have evaluated this endpoint, and yet the relatively weak and inconsistent associations noted by OEHHA and others, this additional justification for the UF is not warranted.

OEHHA identified dozens of studies that examined potential immunotoxicity of PFOA and PFOS, including over a dozen epidemiological studies, numerous animal bioassays, and many supporting in vitro analyses. The database continues to demonstrate weak and inconsistent results, for many of which the biological relevance is unclear. There is natural variation in antibody responses in the human population and epidemiological studies have not reported antibody levels that were below those that are considered protective against disease or that failed to provide a supportive level of

immunity. Furthermore, epidemiology studies have reported inconsistent associations between both PFOA and PFOS and common infections or symptoms (see discussion in ATSDR (2021) and Steenland et al. (2020)) and the National Toxicology Program scored both compounds as 'low confidence' for association with infection disease outcomes (NTP, 2016)."

Response 7: While immunotoxicity was evaluated as a candidate critical effect, OEHHA did not use immune effects as the basis for its HPCs or PHGs for either PFOA or PFOS.

Although OEHHA did not base the PHG on immunotoxicity, OEHHA does not agree with the commenter that the studies taken together are weak and inconsistent. The National Toxicology Program, in their systematic and comprehensive evaluation in 2016 concluded:

> "that PFOA and PFOS are presumed to be immune hazards to humans and to alter immune function in humans. Exposures to PFOA and PFOS are associated with changes in multiple immune outcomes in both experimental animal and epidemiological studies. The strongest bodies of evidence to inform the evaluation of PFOA- and PFOS-associated immunotoxicity are on the antibody response."

Further, US EPA and EFSA both found the data to be of sufficient quality and appropriately sensitive for consideration as the critical toxicity endpoint in humans for PFOA. OEHHA also considered these data when deriving the noncancer health-protective concentration, and the intraspecies UF of $\sqrt{10}$ was included due to the potential concern that immunotoxicity may occur at lower dose levels than hepatic toxicity.

Comment 8: "The total cholesterol endpoint should not be selected as the critical effect, based on current data and understanding of potential modes of action."

"Notably, the decision to rely on increased serum TC to establish a quantitative relationship between PFOS exposure and adverse effect is an outlier when compared with the broad range of public health agencies in the U.S. (both federal and state) (see Table 1 below, based on (ITRC, 2020) and internationally (e.g., Health Canada, Australia/New Zealand) that have reviewed the same human and animal study data on PFOS and selected an alternative endpoint as the basis for health advisories, guidance values, and drinking water maximum contaminant levels for PFOS.

The choice of increased TC as a biomarker of effect from PFOS exposure is questionable from both an empirical basis and a mechanistic basis (i.e., mode of action [MoA]). Numerous epidemiological studies and animal toxicity studies provide data to examine potential associations between serum PFOS levels and blood chemistry (serum and plasma) measures of liver function, such as levels of lipids and liver enzymes. Comprehensive evaluations of the literature, including the summary

presented by OEHHA in the draft PFOA and PFOS PHG document, clearly illustrate the inconsistencies in the empirical data."

"While two large-scale epidemiological studies of participants in the C8 Science Panel studies indicate a positive and statistically significant relationship between risk of abnormal cholesterol levels and PFOS levels (presented as adjusted ratios) in adults (Steenland et al., 2009b) and children and adolescents (Frisbee et al., 2010), inverse and/or non-statistically significant relationships have been observed in a variety of general population studies (Château-Degat et al., 2010; Eriksen et al., 2013; Fisher et al., 2013; Fu et al., 2014; Nelson et al., 2010).

Epidemiologists are aware of the potential for reverse causation associated with and confounding of the serum PFOS/serum lipid relationships, particularly among participants who report using cholesterol- lowering medication. The inconsistent relationship between serum PFOS and TC across studies persists even after controlling for this factor. Australia and New Zealand (FSANZ, 2017) noted that common study limitations of the cross-sectional studies include possible confounding effects (and no adjustments for): 1) co-exposure to PFOA or other PFAS; 2) diet; and 3) glomerular filtration rate (as an index of kidney function)."

"As noted by OEHHA (2021, p.101), in rodent models, including a transgenic mouse model that possesses human-like lipid metabolism, exposure to PFOA tends to reduce cholesterol levels (Pouwer et al., 2019). Health Canada (2018, Section 9.2.2.3 Serum Lipid Effects) provides a synthesis of the animal toxicity study data in monkeys, mice, and rats, the vast majority of which demonstrate an inverse relationship between serum PFOS and TC, LDL cholesterol, HDL cholesterol, and triglycerides. Similar findings were observed in NTP's 28-day toxicity studies of PFAA exposure in rats (Goodrum et al., 2021; NTP, 2019b). This hypothesis is further supported by a recent phase I clinical trial with PFOA, which demonstrated that when human serum levels of PFOA are comparable to the relatively high levels achieved in rodent studies, cholesterol levels decline rather than increase (Convertino et al., 2018).

There is no clear pattern that explains the inconsistency in associations between serum PFAS and TC in both human and animal studies. Factors that may contribute to variability and uncertainty in the study outcomes for PFOS include the dose range, species, sex, and age group. In contrast to most regulatory agencies and independent science advisory panels that examined the same body of science on serum lipid effects, OEHHA appears to have adopted the perspective that a sufficient number of studies with PFOS demonstrate a change in lipid homeostasis, and that collectively these associations are indicative of an adverse effect:

• regardless of whether or not the effect manifests as an increase or decrease in TC;

• despite uncertainty in the clinical significance of the magnitude of the change;

• regardless of whether or not there is consistency within the same study in the associations with other biomarkers of lipid metabolism and liver function; and

• absent supporting animal toxicity data to demonstrate a clear and consistent dose-response relationship."

Response 8: OEHHA has reviewed the work of these other agencies and is aware that some of them have chosen not to use lipid homeostasis as a critical effect. Importantly though, OEHHA has performed its own thorough and comprehensive analyses of this topic, including extensive quantitative and qualitative evaluations of bias, confounding, and causal inference. OEHHA is not aware of any other document that provides as detailed or thorough evaluations as those OEHHA has used to develop its PHGs. Overall, based on this comprehensive assessment, OEHHA has concluded that PFOS adversely affects lipid homeostasis, and that the high quality study by Steenland et al. (2009) provides an excellent source for quantifying this effect (Steenland et al., 2009b).

OEHHA agrees that not every study of PFOS and lipid homeostasis has identified an association. However, many studies have, and several of these are of very high quality. Overall, the weight of the evidence supports a causal effect between PFOS and increased TC, and the basis for this conclusion is described in the PHG draft document (Section 5.3 and pages 206-210).

With regard to confounding by the use of lipid lowering medications, it should be noted that a number of studies have identified associations between PFOS and increased TC or increased low density lipoprotein (LDL) even after excluding people who reported using these medications (Canova et al., 2020; Eriksen et al., 2013; Mattsson et al., 2015; Nelson et al., 2010). This includes the study OEHHA used to calculate its noncancer HPC for PFOS (Steenland et al., 2009b).

With regard to confounding by PFOA, OEHHA assessed this possibility and concluded that major confounding was unlikely (please see Section 6.1.2 of the draft PHG document). For glomerular filtration rate (GFR) and diet, no evidence that these caused major confounding is presented in the comment above and OEHHA could not find any either.

As discussed above, the Convertino et al. (2018) study involved a relatively small number of cancer patients who were unresponsive to traditional treatments (e.g., some may have been very ill) and who received massive doses of APFO (Convertino et al., 2018). Given the uncertainties about the sensitivity of these patients, and uncertainties about whether massive doses of APFO would be expected to have the same toxic effects as more common general population PFOA exposures, the relevance of this study is unknown.

With regard to the other specific comments, OEHHA did consider the direction of the impact on serum lipid levels, and its conclusions were based on ***increases*** in TC or LDL. OEHHA also considered the clinical significance of these changes, and its noncancer HPC for PFOS is based on clinically relevant increases in serum TC (please see Section 6.1.2 of the draft PHG document for a detailed discussion of this issue). Internal consistency within each epidemiologic study was considered. Finally, the animal data were also considered, although the pharmacokinetic differences between laboratory animals and humans (described in Section 5.3 and elsewhere in the draft PHG document) highlight possible reasons why these two species may differ in their response to PFAS.

Comment 9: "There are no biologically plausible genetic reasons why race or ethnicity would represent a more sensitive subgroup for PFOA or PFOS; an additional uncertainty factor to cover human variability is unnecessary.

As noted by OEHHA, the Gallo et al. (2012) study involved a very large number of adults whom likely "included a diverse group of people in terms of ages, health status, smoking and other chemical exposures, nutrition, socioeconomic status and other factors" (OEHHA, 2021, p.182). Although the study did not include children, there is no evidence that children would be more susceptible to changes in alanine transaminase or other effect endpoints related to PFOA or PFOS exposure. The potential additional sensitivity related to race or ethnicity or age to justify an additional UF for intraspecies variation of three is unwarranted."

Response 9: OEHHA agrees there are no specific data on PFOS and lipid homeostasis to suggest that race or ethnicity is a major sensitivity factor. However, there are also no data to suggest otherwise. That is, the research needed to answer this question has not been done. As such, whether or not PFOS-related risks vary by race or ethnicity is uncertain, and therefore an uncertainty factor was applied. It should be noted that this uncertainty factor does not just apply to race and ethnicity. It is also meant to cover uncertainties that could be caused by any other relatively common, but as of yet unstudied, sensitivity factor (e.g., genetics, pre-existing liver disease, medication use, important co-exposures, etc.).

Comment 10: "The use of the default Relative Source Contribution for the noncancer PHGs is inconsistent with currently available data and best practices. OEHHA incorrectly defines the Relative Source Contribution (RSC) term and fails to take into account U.S. and California-specific human data that informs the potential background exposure to PFOA and PFOS. The RSC is defined by OEHHA (OEHHA, 2021, p. 20) as: "the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air)." This is inaccurate. USEPA's guidance on the RSC states that the RSC is "the percentage of total exposure typically accounted for by drinking water… *applied to the RfD*…" (US EPA (2000), p. 1-7; emphasis added). Therefore, the RSC term is used to account for the proportion of *allowable total daily exposure* (i.e., the toxicity value represented by the ADD, also called the reference dose (RfD) by the USEPA, in mg/kg-day) that is attributed or

allocated to drinking water in calculating acceptable levels of chemicals in water. The remainder of the total daily exposure is attributed to other exposure pathways. Therefore, in contrast to OEHHA's assertion, one does not need to be able to calculate individual exposures from all pathways, but rather, one needs to be able to understand how exposure to the general population compares to the ADD, such that the rest of the allowable exposure can be allocated to the drinking water pathway.

US EPA guidance suggests a range of 0.2 to 0.8 for the RSC term (US EPA, 2000). The low-end default value of 0.2 is applied in the absence of chemical-specific data on exposure. It assumes that 80 percent of the target dose can be attributed to exposures other than drinking water and attributes the remaining 20 percent to exposure to drinking water. When data on chemical-specific exposures are available (i.e., the contribution of non-drinking water pathways to total dose) it should be used to develop an alternative RSC.

There have been several studies of dietary, dust, and inhalation exposure to PFOA and PFOS (reviewed in Sunderland et al. (2019)), none of which suggest that exposures other than drinking water are likely to add up to 80% of the allowable daily intakes defined as OEHHA's ADDs. In fact, recent evaluations by several states have applied USEPA's "exposure decision tree method" to derive RSC values of 0.5 for both PFOA and PFOS (Dewitt et al., 2019; Garnick et al., 2021; MNDOH, 2020a; NHDES, 2019). Additionally, most recently, Garnick et al. (2021) estimated an "actual RSC" for PFOA and PFOS of 0.95 based on the 95th percentile background exposures for women based on a 2011 study (Lorber and Egeghy, 2011) and national serum concentration data from the National Health and Nutrition Examination Survey (NHANES).

Importantly, through the Biomonitoring California program, California-specific data are available. According to Minnesota, biomonitoring results such as the NHANES data set can be used to represent non-water or background exposures (MNDOH, 2020b). Chemical-specific data exists for OEHHA to use rather than the default value."

Response 10: There are two approaches included in the US EPA RSC decision tree (US EPA, 2000) – the subtraction approach and the percentage approach – and the choice between the two is driven by chemical-specific considerations. Appendix 4 contains both the US EPA RSC decision tree, and a detailed rationale why the percentage approach was chosen. This determination can be different for different states depending on whether exposure from drinking water is considered a dominant contribution in overall exposure.

OEHHA disagrees with the characterization of Sunderland et al. (2019). These authors reviewed the available literature on source contributions to adult PFAS exposures and found that for 6 available PFOA studies, drinking water contributed to approximately ≤ 20% of total exposure in 5 studies and to 41% in the one remaining study. For PFOS, drinking water contributed to approximately ≤ 20% of total exposure in all 6 available studies. In fact, this analysis supports OEHHA's RSCs of 20% for PFOA and PFOS and

stands in contrast to the comment's statement that in none of the studies, "exposures other than drinking water are likely to add up to 80% of the allowable daily intakes."

To use biomonitoring results in determining the contribution of drinking water to the overall exposure for a specific PFAS, one needs to know PFAS concentrations in drinking water matched to the biomonitoring population. Such data are not currently available from the Biomonitoring California Program.

Comment 11: "OEHHA traditionally utilizes numerous extremely conservative science policy decisions in the derivation of PHGs. Compounding conservative assumptions produce drinking water limits that are a challenge for California drinking water providers to meet and yet offer no increased public health protective measures.

For deriving public health criteria such as a PHG, default, conversative [sic] exposure and toxicity assumptions are typically used. However, the conservative and uncertain toxicity and exposure decisions utilized by OEHHA within the PFOA and PFOS PHG are considerable. They include:

- Applying a 95th percentile consumers-only drinking water intake of 0.053 L/kg-day (OEHHA, 2012). Selection of 95th percentile as the basis of drinking water intake rate is highly conservative. The drinking water intake rate of 0.053 L/kg-day is approximately 22% higher than the 90th percentile consumers-only drinking water intake of 0.0433 L/kg-day identified from the same dataset. Additionally, 0.053 L/kg-day is 70% higher than the equivalent USEPA-recommended drinking water intake for an 80 kg adult.

- Use of linear extrapolation to define the cancer slope factor for both PFOA and PFOS.

- Use of the one in a million (10^{-6}) cancer risk level, the lower end of the "target cancer risk range". For comparison, the USEPA Office of Water lifetime Health Advisories for carcinogenic compounds are based on a 10^{-4} cancer risk level (US EPA, 2018b).

OEHHA should more explicitly communicate the margin of safety that is targeted when applying conservative assumptions at each step of the PHG derivation, including the exposure factors, toxicity reference values, and target cancer risk range."

Response 11: The comment refers to the standard practice by OEHHA which follows established peer-reviewed guidance. The PHG draft document includes references to all applicable guidance documents and in addressing uncertainty of assessment estimates it is stated that the more conservative values of parameters are used.

Low dose linearity is the default assumption in performing dose response analyses (e.g., OEHHA, 2009, p. 28; California Code of Regulations, Title 27, Section 25703(a)).

At US EPA, linear extrapolation to a lower dose in cancer slope factor determination is the default method for carcinogens for which a genotoxic MOA cannot be excluded or when the mode of action is not known, as is the case of PFOA and PFOS. This is articulated in the US EPA Guidelines for Carcinogen Risk Assessment (2005, page 3-21):

> When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained.

US EPA health advisories should not be compared to PHGs, but to California NLs. PHGs are equivalent to US EPA's MCLGs, which are set to zero for genotoxic carcinogens. While developing MCLGs, US EPA also determined cancer slope factors for PFOA and PFOS using linear extrapolation (US EPA, 2023). The comment is incorrect in claiming that US EPA's health advisories are set at 10^{-4} risk of cancer. Concentrations corresponding to the 10^{-4} risk of cancer are indeed included in the US EPA's Drinking Water Standards and Health Advisories Table but only as a comparison to the MCLs and Life-time Health Advisories which are typically much lower (US EPA, 2018b).

Comment 12: "CASA appreciates the opportunity to communicate our concerns to OEHHA on this important regulatory development within the state. OEHHA's draft document, in many ways, represents the most comprehensive and robust recent compilation of relevant information related to PFOA and PFOS potential human health risks. However, OEHHA's draft PHGs contain overly conservative misrepresentations of the PFOA/PFOS-related science, resulting in proposed PHGs that are not consistent with the available science and best standards of practice.

- The PHGs should be based on noncancer endpoints.

- The weight-of-evidence for cancer effects for PFOS demonstrates that the compound is unlikely to present a carcinogenic risk at low levels.

- OEHHA's conclusions that PFOA and PFOS are genotoxic conflicts with conclusions from numerous other organizations and the available data.

- OEHHA misapplies the IARC key characteristics of carcinogens and should not use them as supporting evidence for cancer-based PHGs.

- The human data used to derive the PFOA PHG is highly uncertain.

- The use of the default RSC for the noncancer PHGs is inconsistent with currently available data and best practices.

• The use of conservative default science policy decisions in combination with conservative interpretations of the science for PFOA and PFOS results in highly conservative yet imprecise draft PHGs."

Response 12: OEHHA acknowledges the comment but does not agree with the opinions stated. Each of the specific statements is addressed in the Responses above. See responses to Comments 2, 4, 5, 6, 7, 10, and 11 from CASA.

CALIFORNIA COUNCIL FOR ENVIRONMENTAL AND ECONOMIC BALANCE

Comment 1: "As it relates to OEHHA's proposed PHG values for PFOA and PFOS, CCEEB and its members have concerns about the transparency associated with and quantity of the studies relied upon as well as whether they were sufficiently robust and subject to adequate peer review. The issue of transparency, in particular, has been the subject of prior discussion as it related to OEHHA's development of the reference exposure levels (RL) and notification levels (NL) for PFOA and PFOS, most recently in the context of legislation on the issue.

Ultimately, the process by which OEHHA determines the studies to be relied upon as well as the studies themselves must uphold the highest integrity and be based in the best available, sound, current, and appropriately peer-reviewed science, principles and methods used by experts in relevant disciplines (i.e. toxicology, epidemiology, etc.). Further, such studies should hold relevance to and data associated specifically with human exposure and consumption of PFOA- and PFOS-impacted drinking water, particularly given the PHGs' basis for MCL-setting by the SWRCB."

Response 1: OEHHA acknowledges the comment.

Comment 2: "Source Contribution, Declining Use Warrants Reevaluation

As California and other states have moved to ban the use of PFOA and PFOS across an array of applications, the expectation is that over time this will result in decline in these chemicals' pervasiveness in groundwater. While this may be a background level issue, it is nonetheless relevant to the expected use of the PHG in the MCL-setting process. To that end, OEHHA should be clear as part of its PHG-setting for these chemicals that the values will be reevaluated as the use of PFOA and PFOS and the expected decline in the frequency of detections and concentrations detected, and as related science evolves. This is important, as we would expect to see a decline in the body burden, health effects, and exposure levels, which may at some point warrant a higher value based on the "lifetime of exposure" criteria that OEHHA is required to use to set its values."

Response 2: State law requires PHGs to be regularly re-evaluated. However, neither the PHG draft document nor its future updates would directly depend on the frequency of detection and detected concentrations of PFAS in drinking water. PHGs are based solely on health considerations. It is not clear what the "lifetime of exposure" criteria are, to which the comment refers. The Statute requires PHGs to consider bioaccumulating properties of pollutants, or in other words, "the relationship between exposure to the contaminant and increased body burden" (Health & Safety Code section 116365(C)(1)(c)(iii)), however it would be incorrect to interpret this language as an exposure level-dependent decision tree in PHG development.

Comment 3: "Human Right to Water

While CCEEB would like to reiterate that the PHG must be set based on human health effects alone, it should be noted the PHG level will ultimately have an impact on the Human Right to Water. A lower PHG level that ultimately results in a lower MCL concentration can be anticipated to increase costs for water, and would be likely to result in water resources being decommissioned until such time as technological advances allow for treatment to the corresponding low MCL levels. These would be unfortunate unintended consequences of OEHHA's well-intentioned effort to establish PHGs, if those PHGs were to be based on an inadequate scientific basis."

Response 3: The commenter is correct in stating that PHGs are solely based on human health considerations. The rigorous process for developing PHGs, which includes public and external scientific peer review, ensures that these values have sound scientific bases. Economic and technological feasibility are considered by the Water Board when setting MCLs.

CLEANEARTH4KIDS.ORG

Comment 1: "Thank you for your important and urgent work to review to set the limits PFOS and PFAS in drinking water. Access to clean water is a basic human right and foundational for good health and survival."

Response 1: OEHHA acknowledges the comment.

Comment 2: "CleanEarth4kids.org asks you to set the Public Health Goals (PHGs) for PFOA, PFOS and all PFAS in drinking water at 1 ppt.

PFAS must be treated as a class. DTSC has already determined "regulating individual PFAS is ineffective" and California treats them as a class as shown by SB343, AB1200, AB1201 which were signed by Governor Newsom on Oct 5, 2021.

Perfluoroalkyl and polyfluoroalkyl substances, called PFAS, are a class of almost 5,000 synthetic chemicals found in many products like food packaging, waterproofing sprays, household cleaners, stain resistant carpet, nonstick cookware and fire-fighting foam. PFAS as a class share many characteristics and toxicity."

"Please protect Californians and set a strong precedent for other states. Please set PHGs for all PFAS in drinking water at 1 ppt."

Response 2: While toxicological effects of PFOA and PFOS are somewhat similar, their resulting PHG values are notably different. It would not be possible to propose a single value for combined PFOA and PFOS that would be equally health protective and not overly conservative. In the last several years, OEHHA has released individual health assessments for several PFAS, while work on the feasibility of developing combined PFAS PHGs is ongoing.

A PHG of 1 ppt for a mixture of PFAS would not be particularly health-protective for PFOA because cancer risk at this concentration would be 1 in 7,000 when compared to the proposed PHG, which is based on a 1 in 1 million cancer risk.

Comment 3: "PFAS including PFOS and PFOA remain unregulated and continue to be used. Research shows widespread PFAS contamination of drinking water and studies by the CDC showed at least 12 PFAS in the blood of almost all Americans.

A new study by the Environmental Working Group (EWG) released in October 2021 has identified almost 42,000 possible sources of PFAS pollution in water. Those responsible must be identified and required to not only stop their pollution, but pay for the filtration required to remove PFAS from our precious water."

Response 3: OEHHA acknowledges the comment.

COMMUNITY WATER SYSTEMS ALLIANCE

Comment 1: "Our first comment concerns the drinking water regulatory process followed in California and the paradoxically negative public health consequences that flow from a flawed process. In theory, regulation should follow a pure, scientifically sound procedure with abundant, peer-reviewed and universally accepted data, resulting in a clear message that is understood and trusted by the regulated community and the public. In California, however, the process creates underground regulation, confuses the public, reduces confidence in the drinking water supply, and imposes an impossible burden on communities least capable of meeting the regulations. Public Health Goals, along with Notification and Response Levels, and how they are misused, are partially to blame for this. The PHGs for these two PFAS will perpetuate this cycle.

The preface to the First Public Review Draft describes the relationship of PHGs to the rest of the regulatory process:

PHGs published by OEHHA are for use by the State Water Resources Control Board (SWRCB) in establishing primary drinking water standards (California Maximum Contaminant Levels, or CA MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, MCLs adopted by SWRCB consider economic factors and technological feasibility. State law requires that MCLs be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory and represent only non-mandatory goals.

PHGs "represent only non-mandatory goals," and "provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime" (PHG Draft, p. 2). Significantly, the Notification Levels adopted by OEHHA two years ago are set at 0.0051 µg/L (PFOA) and 0.0065 µg/L (PFOS). While the Maximum Contaminant Level to be set by the State Water Board should consider technological and economic feasibility, in practice Notification Levels and Response Levels are treated as de facto enforceable standards by some state agencies. For example, the Division of Drinking Water has refused to approve operating permits for some new water treatment systems if treatment for PFAS is not also included, despite having no Maximum Contaminant Level for the substances. Conversely, the California Public Utilities Commission prohibits investor-owned utilities from recovering costs for PFAS treatment, since there is no enforceable MCL.

Adding to the regulatory muddle and public confusion, water agencies are required to report exceedance of PHGs on their Consumer Confidence Reports, and to hold public hearings (https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/CCR.html accessed 8/31/21). This in turn is often misconstrued, raising alarm in an unwitting public and undermining trust in the drinking water supply (https://www.ewg.org/research/national-pfas-testing/). Low-income consumers, who

may have lower educational attainment, are most affected and harmed by mistrusting the safety of tap water (Family et al., 2019)."

Response 1: PHGs are health-based values and are not enforceable. OEHHA does not have authority over the development and enforcement of drinking water standards, or monitoring and reporting of contaminant levels in drinking water.

Comment 2: "Finally, laboratory testing at the very low levels of these PHGs are at the very edge of what is possible, difficult to perform, not widely available, and expensive. Setting a PHG at 0.007 parts per trillion implies that such measurements are routine and widely accessible, but in fact they are cost-prohibitive for many small systems. OEHHA should consider real-world consequences of setting this numerical level."

Response 2: PHGs are based solely on health considerations and issues regarding analytical methods, detection limits and reporting requirements have no bearing on the derivation of these values. However, the factors noted by the commenter can be taken into account in the establishment of MCLs by the Water Board.

US DEPARTMENT OF NAVY

Comment 1: "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)."

Response 1: The proposed PFOA and PFOS PHGs are based on cancer. The resulting health-protective concentrations are developed using cancer slope factors and do not rely on the use of uncertainty factors. The proposed health-protective concentrations for noncancer effects of PFOA and PFOS, also developed in the draft document, were derived using combined uncertainty factors of $\sqrt{10}$ and 10, respectively, not 300.

By law, PHGs are based exclusively on public health considerations and OEHHA cannot incorporate risk management factors in the PHG development process. Thus, OEHHA does not consider detection limits when developing PHGs.

The rigorous process by which the PFOA and PFOS draft PHGs have been developed, which includes public and external scientific peer review, ensures OEHHA is using the most current principles and methods in the field and the proposed PHGs are based on the best available scientific data.

Comment 2: "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."

Response 2: The HRs in the two highest exposure categories in Barry et al. (2013) were statistically significant in community members, and these results did show a dose-response trend (Barry et al., 2013). While the p-trend was not statistically significant, the HRs clearly increased as the exposure levels increased (i.e., odds ratios of 1.0 (reference), 1.34, 1.95, and 2.04 with increasing quartiles of exposure). With regard to the lower two exposure levels in Vieira et al. (2013) please see the response to Comment 11 from the American Chemistry Council.

Comment 3: "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."

Response 3: In response to this comment, the potencies are now expressed in the same units, $(mg/kg\text{-}day)^{-1}$.

Comment 4: "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 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."

Response 4: The PFOA and PFOS acceptable daily doses (ADDs) were derived from human studies; ADDs were not calculated from animal studies due to the availability of human data. For noncancer ADDs based on human data, OEHHA used a UF of approximately 3 (i.e., $\sqrt{10}$) for PFOA to account for residual inter-individual variability (e.g., the critical study did not include children, was not diverse in terms of race or ethnicity, and did not examine other potential susceptibility factors such as obesity or genetics) and 10 for PFOS ($\sqrt{10}$ to account for use of LOAEC instead of NOAEC and $\sqrt{10}$ for residual inter-individual variability). Thus, OEHHA did not use the combined UF of 300 and an interspecies UF was not applied. OEHHA's rationale for the use of these UFs is presented in Section 6.1 of the draft PHG document.

Comment 5: "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."

Response 5: It is OEHHA's policy to use the linearized multistage model for cancer, and the BMDS outcomes for these analyses are included in Appendix 10.

For noncancer endpoints, only the outcomes and model parameters for the best fitting models for each endpoint of interest are included in Appendix 10. OEHHA's BMDS analysis, including model selection follows existing guidelines (OEHHA, 2008; US EPA, 2012). OEHHA chose not to include all model descriptions from the conducted BMDS analyses, as this would add an excessive number of pages of detailed technical information to an already extensive document.

Comment 6: Referring to Section 4.1, page 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."

Response 6: In response to this comment, clarification has been added in Section 4.1.

Comment 7: "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."

Response 7: In response to this comment, more detailed analysis of the Seals et al. (2011) dataset has been to Section 4.7 of the draft PHG document. The $T_{1/2}$ estimates derived in the studies of discontinued exposure are often complicated by the lack of background adjustment or inadequate adjustment. While Seals et al. (2011) adjusted for constant background exposure (subtracting 5 ng/mL or 15 ng/mL from serum levels), background PFOA levels in the US population drastically declined from the eighties through early 2000s, which spanned the exposure period of the analyzed data set. To

correctly adjust for the declining background levels, higher background values would have to be applied to persons with a longer post-exposure period compared to the persons with a shorter post-exposure period. In the absence of such an adjustment, the regression would bias toward a shallower slope and a higher $T_{1/2}$ estimate. Thus, it is not clear how much of a higher PFOA $T_{1/2}$ value would be due the uncertainty in the background adjustment. All other studies that produced higher PFOA $T_{1/2}$ suffered from similar or worse background adjustment issues. In contrast, studies based on higher initial exposures, such as Li et al. (2018) are not subject to background effects. While it would be optimal to base $T_{1/2}$ and clearance estimates on exposures that are more similar to those observed in California residents, there is currently no adequate analysis of such data available in the scientific literature. While Table 4.7.1 and other datasets in the PHG draft document list all available estimates for TK parameters, the choice of a specific value was based on the analysis of the quality of the studies (as described in the text of the document) and not on picking the most conservative value of the set.

Comment 8: Referring to Section 5.1.4, page 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."

Response 8: The comment refers to the sentence, "However, although not explicitly stated, there is some indication that the laboratory personnel measuring the PFAS levels in the Faroe Islands studies were blinded to the outcome status of the participants (e.g., mention is made of "coded" laboratory samples, and PFAS and antibody levels were measured in different labs) (Grandjean et al., 2012; Grandjean et al., 2017)." OEHHA has considered this commenter's concern but has determined that rather than basing conclusions on a simple single assumption, it was best to examine the issue in more detail. In OEHHA's extensive experience with laboratory samples, it was determined that it would be highly unusual for "coded" samples to be coded with obvious information on the outcome or exposure being studied (they are almost always coded with a subject identification number or bar code). Given this, while it is possible that bias from non-blinding might have occurred, it seems incredibly unlikely, and an assumption that it did occur would seem to be at least somewhat misleading.

Comment 9: "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."

Response 9: OEHHA agrees that the main focus of Miller et al. (2009) is on thyroid hormones (Miller et al., 2009). However, the basic principles presented in this paper apply to almost any important adverse effect, including hepatotoxicity. As a whole, this paper provides excellent, thoughtful, and well-described examples of how relatively small effects in otherwise healthy individuals can have tremendously important effects on a population basis. This is the point being made in the section of the PHG document in which Miller et al. (2009) is referenced, and as such, this publication is directly relevant to the discussion there. Regardless, in response to this comment, Section 5.2.5 (formerly Section 5.2.4) has been revised to point out that Miller et al. (2009) focuses on thyroid hormones but that the same principles also apply to liver toxicity.

Comment 10: "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, TableA7.12).

'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."

Response 10: An extensive discussion of the likely effects that PFOA has on PFOS-TC associations is included in the PHG document (Section 6.1.2). As noted, the correlation between PFOS and PFOA in the study used by OEHHA to calculate the noncancer HPC for PFOS was only modest (Steenland et al., 2009b). That is, it was at a level unlikely to cause major confounding (Axelson, 1978). In addition, the magnitude of the

association between PFOS and TC in this study appeared to be generally greater than that for PFOA, which is additional evidence that PFOA was not the sole cause of the associations reported for PFOS. Finally, the authors of this study reported that when both PFOA and PFOS were included in the same statistical model, the PFOS-TC association was only modestly attenuated. This provides even further evidence that PFOS has its own effect, independent of PFOA. Overall, while OEHHA agrees that it is possible that some of the effect ascribed to PFOS could be due to PFOA, this contribution is likely to be small and unlikely to introduce major bias into the HPC calculations.

Comment 11: "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 (20201) 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 Cl 1 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."

Response 11: As noted in the response to Comment 39 by 3M, while EFSA expressed concern about a common enterohepatic cycling pathway, they provided no research or other justification supporting this concern (EFSA, 2020). The Donat-Vargas et al. (2019) publication cited by the commenter was already included in OEHHA's evaluations and in the draft PHG document (see Tables A7.7, A7.8, A7.10 and A7.11). While this study did not show clear evidence of an association between PFOS and TC, a number of

other high quality studies did. These are reviewed and referenced in Section 5.3 and in Tables A7.8 and A7.11 of the draft PHG document.

The study by Salihovic et al. (2020) involved only 20 participants but assessed over 400 different associations (Salihovic et al., 2020). As such, this study was described as a "proof-of-concept" study by its authors, and its results need to be further explored and replicated before they can be used to make any firm conclusions.

The L-FABP data cited by the commenter is from a study in rats and it is unknown if these same effects occur in humans. In addition, it is not clear how this mechanism could explain how small changes in serum cholesterol could cause such large changes in serum PFOS, like those seen in the study OEHHA used to develop its noncancer HPC (Steenland et al., 2009b). This mechanism would also not explain how a study using an external metric of exposure could still find an association between PFAS and higher serum lipid levels (Winquist and Steenland, 2014). Please see the more detailed discussion of these issues in Section 6.1.2 of the draft PHG document.

Comment 12: "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., 2002), 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, 2018). 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.

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."

Response 12: OEHHA considered IARC (2017) in its literature analysis and overall assessment of mechanistic data. OEHHA identified several positive genotoxicity studies for PFOA, either mentioned in IARC (2017) or published subsequent to its release. OEHHA agrees (and states in the PHG draft) that the overall mutagenicity evidence is weak. However, given a sizable fraction of positive genotoxicity studies overall, one cannot exclude a genotoxic mechanism of PFOA carcinogenesis, at least as a possible contributing MOA. Because the MOA is not known, the default linear extrapolation method is used for the PFOA PHG calculation.

Comment 13: "OEHHA used increases in liver enzymes (specifically, ALT) as the basis for its non- cancer RID 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), '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. [sic], 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).

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)(Olsen et al., 2000; Olsen et al., 2007). There is also little evidence of frank liver disease in 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.

Recommend that OEHHA revisit and expand the biological significance and larger body of evidence for PFOA and liver enzymes."

Response 13: Gallo et al. (2012) made the statement cited by the reviewer without providing any supporting evidence or rationale (Gallo et al., 2012), and the commenter provides none either. Similarly, Darrow et al. (2016) provided no convincing evidence to support the mechanism they proposed, and it's unclear how this mechanism could plausibly cause the Gallo et al. (2012) findings. In other words, Gallo et al. (2012) reported that an 11% increase in ALT was associated with an over 5,000% increase in PFOA, and neither Darrow et al. (2016) nor the commenter have explained how such a relatively small increase in ALT could cause such a massive increase in serum PFOA. Without a plausible explanation for this, any claim that reverse causation was responsible for the Gallo et al. (2012) results seems unfounded.

OEHHA agrees that "interpreting abnormal liver enzymes requires an understanding of the clinical context." As such, OEHHA has provided a detailed discussion of the clinical relevance of the Gallo et al. (2012) findings (Section 6.1.1 of the draft PHG document). As noted and referenced in this discussion, the elevations in ALT levels evaluated by Gallo et al. (2012) have been associated with major increases in both liver disease and mortality.

Please see the discussions of the occupational studies of ALT and of studies of liver disease in response to Comments 14 and 16 by 3M above.

The commenter has concluded here that Gallo et al. (2012) has "many limitations." However, only a few potential ones are listed in this comment, and no clear evidence is provided that any of these had a major impact on this study's findings. OEHHA has thoroughly reviewed the Gallo et al. (2012) study (please see Section 6.1.1 of the draft PHG document) and has concluded that this is a high quality study and its results represent important and real effects.

Comment 14: "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."

Response 14: The cross-sectional design of the studies mentioned by the reviewer is a *potential* limitation. However, this is much different than an *actual* limitation. Careful evaluations are needed to distinguish the two, and this is what OEHHA has done. As discussed in Section 6.1.1 of the draft PHG document, the cross-sectional design used by Gallo et al. (2012) is unlikely to have been a major limitation (Gallo et al., 2012). It is also important to note that Gallo et al. (2012), and not Abraham et al. (2020), was used as the basis of the PFOA noncancer HPC (Abraham et al., 2020). Because of this, OEHHA presented much more detailed evaluations of Gallo et al. (2012). Finally, the comment above contains incorrect information about the findings of Abraham et al. (2020). This study did find diminished responses to tetanus and diphtheria vaccinations.

Comment 15: "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 RID. 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."

Response 15: OEHHA agrees that there is some intra-individual variability in serum cholesterol levels. However, because these levels were measured using the same methods in all subjects, the resulting bias is most likely to be towards the null, not towards the positive effects reported in Steenland et al. (2009) (Steenland et al., 2009b). The commenter suggests that diet could be an important confounder but provides no evidence or justification to support this assertion. In addition, no particular dietary variable is identified. OEHHA evaluated this issue and concluded that major confounding by diet is unlikely. Regarding cardiovascular disease, please see the response to Comment 44 by 3M above.

Comment 16: "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."

Response 16: The possibility that asbestos is an important confounder is already discussed in the draft PHG document (Section 6.2.1). For asbestos to be an important confounder it would have to both be strongly linked to PFOA exposure and the relative risks between asbestos and kidney cancer would have to be very high (e.g., much greater than 2.0) (Axelson, 1978). While there is some indirect evidence that PFOA could be related to asbestos exposure in Steenland and Woskie (2012), there is no evidence for this in any of the other studies that have identified links between PFOA and kidney cancer (Shearer et al., 2021; Vieira et al., 2013; Barry et al., 2013). This includes the population based studies in the C8 area where there is no evidence of widespread high asbestos exposure among the general population (Vieira et al., 2013; Barry et al., 2013). In addition, while some studies have linked asbestos to kidney cancer, this evidence is not consistent across all studies (IARC, 2012). In fact, no association between asbestos exposure and renal cell carcinoma was observed in the study cited by the commenter (Karami et al., 2011). Perhaps more importantly though, there is no evidence that the association between asbestos and kidney cancer (even if one does exist) is anywhere near high enough to cause the PFOA-RCC associations reported in any of these studies (Axelson, 1978). Overall, there appears to be little to no support for the statement that "three of the four studies used to support the association between PFOA and RCC are confounded by asbestos exposure."

Comment 17: "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 interpreted in such a way that PFOA exposure may be associated with a significant portion of the national average RCC incidence.

Please consider further clarifying this section, particular if its meant to indicate that PFOA exposure may be responsible for a considerable portion of national RCC incidence."

Response 17: In response to this comment, Section 6.2.1 has now been clarified to note that these particular calculations were only intended to evaluate selection bias and were not for any other purpose.

Comment 18: "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."

Response 18: Basing conclusions solely on statistical significance can be fraught with errors (Greenland et al., 2016), and the results cited above should be discussed in their proper context. As reviewed in Section 6.2.1 of the draft PHG document, Shearer et al. (2021) provides very good evidence that the association between PFOA and renal cell carcinoma reported in this study was not confounded by other PFAS. If significant confounding by other PFAS did not occur then there is no good reason to include these other PFAS in the final PFOA-RCC models. In fact, there is a very good reason not to do so; multi-collinearity and the loss of precision would result from this. For these reasons, the Shearer et al. (2021) results that are unadjusted for other PFAS were considered the most valid and appropriate for cancer slope factor calculations, and these are what OEHHA has used. In response to this comment, additional discussion of this issue has now been added to Section 6.2.1 (under *Results*) of the draft PHG document. Also, please see the response to Comment 6 from the American Chemistry Council and others.

Comment 19: "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 tetrafluoroethylene 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 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.

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."

Response 19: The kidney cancer HR for community members in Barry et al. (2013) was 2.04 (95% confidence interval (CI), 1.07-3.88) for participants in the highest exposure category (Barry et al., 2013). Although the p-trend was not statistically significant, the HRs clearly increased as PFOA exposure increased (HRs of 1.00 (reference), 1.34, 1.95, and 2.04 for quartiles 1 to 4, respectively).

Regarding the comments about Steenland and Woskie (2012), please see the response to Comment 4 from 3M. The Consonni et al. (2013) study was not skimmed over and in fact is mentioned in several places throughout the draft PHG document.

When one study, such as Raleigh et al. (2014), reports findings that are dramatically inconsistent with those of all other studies of the same issue, then it is appropriate (and necessary) for risk assessors to go to great lengths to explore the possible reasons why. This is what OEHHA has done. The general statement that the cohort design is "stronger" than the case-control design is unsupportable. Each study should be evaluated on its own merits and this is also what OEHHA has done. The conclusion that the healthy worker effect does not affect cancer risks is also unsupportable and the commenter has not provided any evidence that this is the case. The all-cause and all-cancer SMRs in the PFOA exposed plant in Raleigh et al. (2014) were 15-20% lower than the corresponding SMRs in the unexposed comparison plant (Raleigh et al., 2014). Given that the outcomes for these SMRs are death and cancer, both of which are very common and very serious, OEHHA considers this difference substantial.

Comment 20: "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."

Response 20: Raleigh et al. (2014) used an exposure model that was not evaluated using a formal validation study (Raleigh et al., 2014), and no actual validation data is presented in the comment above. Serum samples were collected in a relatively small number of workers, but again, these were not used to formally or directly validate the exposure model. The lack of validation data for this study is already discussed in Section 6.2.1 of the draft PHG document.

Comment 21: "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 greater incidence of kidney cancer than an unexposed population in the Raleigh et al. study.

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."

Response 21: It should be noted that the studies by Vieira et al. (2013) and Shearer et al. (2021), and not the study by Steenland and Woskie et al (2012), were used as the basis of OEHHA's cancer slope factor calculations. The arguments presented in the comment above about Steenland and Woskie (2012) do not contradict OEHHA's conclusions that the highest exposure categories in Raleigh et al. (2014) contained very few cases. They also do not contradict OEHHA's conclusions that Raleigh et al. (2014) had a number of other important potential weaknesses including uncertainties regarding the comparison population, uncertainties about the exposure models, and others.

Comment 22: "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."

Response 22: If presented by themselves and without the proper context, OEHHA agrees that these two statements may seem contradictory. However, OEHHA did not present these statements in isolation, and the context in which they are presented is important. OEHHA has reviewed these two statements and the context in which they were presented, and concludes that both statements are valid and not contradictory.

Comment 23: "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."

Response 23: The following statement in the comment above is consistent with OEHHA's conclusions that PFOA causes kidney cancer and that these effects might be widespread:

> *"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."*

OEHHA chose to use the lifetime kidney cancer risk in males rather than in both sexes or in females because the former was the more conservative estimate. As shown in Appendix 13, while the general US cancer rate could be somewhat of an overestimate for the PHG calculations, its impact on these calculations was likely to be relatively small.

Comment 24: "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."

Response 24: As the comment correctly notes, OEHHA followed its guidelines in selecting 5% BMR in cancer dose-response analysis and in conducting a multi-site

tumor dose-response analysis. The comment does not provide any information that would support modification of the guidelines in these cases. Justification for these methods can be found in OEHHA's peer-reviewed guidance documents (OEHHA, 2008, 2009).

Comment 25: "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 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.

Please consider whether an alternative RSC would be appropriate for the PHG derivations."

Response 25: In determining the RSC, OEHHA followed the US EPA decision tree (US EPA, 2000), and OEHHA's rationale for selecting an RSC of 20% is clearly outlined in Appendix 4. Different states and exposure situations may have different rationale for RSC selection. For California, it is not evident that drinking water is the primary source of PFOA and PFOS, and there are no data to support this assertion. Similarly, there are very limited California-specific exposure data on PFOA and PFOS from other sources, such as food or indoor dust. Because of this uncertainty, a default value of 20% was selected. Please see above response to Comment 10 from the California Association of Sanitation Agencies.

Comment 26: "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."

Response 26: OEHHA agrees that PFOA and PFOS have demonstrated a decreasing trend in serum levels that likely reflects decreasing exposures. However, there is no evidence to indicate that exposure from drinking water lags behind other sources of exposure in this hypothetical decrease. Review of available data indicates that generally (outside the cases of highly contaminated drinking water), drinking water contributes ≤20% of overall exposure to PFOA and PFOS. Based on information available in California and the US EPA RSC Decision Tree, OEHHA also determined that 20% is

the most appropriate RSC for PFOA and PFOS. See also response to comment 10 from the California Association of Sanitation Agencies.

Comment 27: "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, 194-1996, 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).

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."

Response 27: OEHHA uses drinking water intakes that were independently developed and scientifically peer-reviewed (OEHHA, 2012). OEHHA assumed an average body weight of 70 kg, and the resulting 95th percentile direct and indirect water consumption rate is 3.7 L/day. For comparison, the latest US EPA update to its *Exposure Factors Handbook* Chapter 3 provides 95th percentile for water consumption corresponding to 3.0 L/day (rounded) (US EPA, 2019b). The difference is less dramatic than the 2-fold difference that the comment states. OEHHA (2012) addresses the differences in drinking water rates with the US EPA values. The commenter is also referred to OEHHA's detailed discussion of the data supporting its drinking water rate in Appendix 3 of the draft PHG document.

Comment 28: "The language in the final paragraph on this page [p. 628, Appendix 12] 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."

Response 28: In response to this comment, this section in Appendix 12 has been rewritten to improve clarity.

ENVIRONMENTAL WORKING GROUP et al.[9]

General Comments: "Our organizations support the scientific analysis and offer suggestions for improvement to further protect human health.

- We support OEHHA's analysis of the most recent science and its use of the best available data and most current principles to arrive at the conclusion that a safe level of exposure to PFOA or PFOS is likely 1 ppt or lower, and significantly below the current EPA health advisory of 70 ppt.
- We support the evaluation and use of human epidemiological evidence of harm for both the PFOA and PFOS assessments.
- We suggest that OEHHA use the most health protective study in setting the public health goal for PFOA.
- We suggest to the State Water Resources Control Board that PFAS be evaluated as a class and support establishing a class-based public health goal for PFAS."

Response: OEHHA acknowledges the comment.

Comment 1: "We strongly support the use of human epidemiological data that links PFOA to kidney cancer as the basis for the public health goal. This is similar to OEHHA's development of the public health goal for arsenic using human exposure data. These assessments are in accordance with the EPA's Guidelines for Carcinogenic Risk Assessment:

'Epidemiologic data are extremely valuable in risk assessment because they provide direct evidence on whether a substance is likely to produce cancer in humans…When human data of high quality and adequate statistical power are available, they are generally preferable over animal data and should be given greater weight in hazard characterization and dose-response assessment, although both can be used' (US EPA, 2005).

Both human epidemiological studies used in OEHHA's dose response analysis had large numbers of participants with representative exposure levels of the general population. The study by Shearer et al. included renal cell carcinoma cases identified from a randomized screening trial of 150,000 adults, and Viera et al. identified cases from 13 counties in Ohio and West Virginia from an estimated population study area of 500,000. PFOA exposure was assessed directly using measured serum levels of individuals (Shearer et al.), a good indicator of long-term exposure, and Viera et al. estimated PFOA levels using a validated exposure model. Both studies showed

[9] Sierra Club, Clean Water Action, Upstream, National Resources Defense Council, National Stewardship Action Council, Leadership Council For Justice And Accountability, Center For Public Environmental Oversight, Green Science Policy Institute, Integrated Resource Management, Erin Brockovich Foundation, Center For Environmental Health, Heal The Bay, Women's Voices For The Earth, Pfas Action Group, Calpirg, Community Water Center, Responsible Purchasing Network, Breast Cancer Prevention Partners, Healthy Babies Bright Future

evidence of a dose-response relationship. The findings of these studies are also consistent with two other human studies that show a strong association between PFOA and kidney cancer (Barry et al., 2013; Steenland and Woskie, 2012).

We agree that studies in animals also support the carcinogenicity of PFOA to humans. The National Toxicology Program's 2020 report "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Perfluorooctanoic Acid (CASRN 335-67-1) Administered in Feed to Sprague Dawley Rats" concluded, following two-year feeding studies, that PFOA causes cancer in male rats. The NTP study found "clear evidence of carcinogenic activity" and that PFOA exposure increased the incidence of tumors in liver and pancreas in male rats. The NTP findings supported the proposed listing of PFOA as a carcinogen under California Proposition 65, as previously determined by OEHHA this year (https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-chemical-authoritative-bodies-mechanism- perfluorooctanoic).

We support the use of animal studies to develop the public health goal for PFOS, as no large sample-size epidemiology studies were identified to rigorously calculate human cancer risk. However, epidemiological studies were used to calculate non-cancer risk based on findings from the C8 study and the association of increased risk of elevated cholesterol. Recently Li et al. also found causal association of serum levels of PFOA, PFOS and PFHxS and elevated cholesterol (Li et al., 2020a)."

Response 1: OEHHA acknowledges the comment.

Comment 2: "In setting the proposed public health goal value for PFOA based on increased kidney cancer risk, OEHHA averaged the results from two different studies that found increased risk in the general population. As OEHHA noted in its analysis of biases in the epidemiologic studies, it was likely that problems related to participant recruitment and selection, categorizing exposure, and classification of those without kidney cancer all likely led to underestimates, not overestimates, of cancer risk. The justification for the use of the geometric mean as opposed to the most protective cancer slope factor is inadequate and described in the text as being used to 'make maximum use of both these strong studies.'

The most protective cancer slope factor should be used to calculate the public health goal so that it is designed to protect the most vulnerable populations, as required by statute, and the additional study or studies should be used as supporting evidence."

Response 2: The two studies used by OEHHA to calculate the PFOA HPC for cancer were judged to be of similarly very high quality overall and of similarly very high quality in their ability to provide accurate information on dose-response (Shearer et al., 2021; Vieira et al., 2013). In more simple terms, both were excellent studies, and one was not better than the other. For this reason, OEHHA sees no clear justification for excluding either study or in judging that one was likely more sensitive than another. In response to this comment, a note regarding this issue has now been added to Section 6.2.1 of the draft PHG document.

Comment 3: "Although we understand that OEHHA developed the proposed public health goals for PFOA and PFOS at the request of the State Water Resources Control Board, this only represents a small step toward protecting public health. Consequently, our organizations urge the State Water Board and OEHHA to prioritize review of PFAS beyond the long-chain PFAS compounds to include those still in widespread active use, and most comprehensively, the entire class of chemicals. California's Environmental Contaminant Biomonitoring Program lists the entire class of PFAS as priority chemicals for measuring it in the blood and urine of Californians. The Department of Toxic Substances Control also applies the class approach to prioritizing chemicals within the Safer Consumer Products program and supports extending this approach to other regulatory agencies to focus on this entire class of chemicals with similar hazard traits (Bălan et al., 2021). This framework is necessary to avoid regrettable substitutions and manage a persistent, structurally similar class that includes thousands of chemicals (Kwiatkowski et al., 2020). Further, other PFAS that have been studied, beyond PFOA and PFOS (Butenhoff et al., 2012a), such as the replacement chemical GenX (Caverly Rae et al., 2015), have shown evidence of carcinogenicity in two-year animal studies.

Our organizations are deeply concerned about the prevalence of all types of PFAS detected in drinking water and the continued widescale persistence in the environment. Analyzing state and federal data, it is estimated that more than 200 million Americans (Andrews and Naidenko, 2020), including up to 16 million Californians (https://www.nrdc.org/resources/dirty-water-toxic-forever-pfas-chemicals-are-prevalent-drinking-water- environmental), could have PFAS-contaminated drinking water. Analysis has also identified more than 40,000 industrial or municipal sites that are potential sources of PFAS contamination across the nation, as of July 2021 (https://www.ewg.org/interactive-maps/2021_suspected_industrial_discharges_of_pfas/map/). In addition to the environmental exposures to PFOA and PFOS that continue to affect the health and safety of California's residents despite their phase-out, there is growing evidence that the replacement chemicals that continue to be approved for use are just as harmful to human health and the environment. A peer-reviewed study released in 2019 refutes claims by the chemical industry that the next generation of PFAS is safer than PFOA and PFOS (Li et al., 2020b). For instance, GenX and PFBS have been linked to health effects similar to those caused by the chemicals they have replaced (PFOA and PFOS, respectively) (US EPA, 2018a).

Due to income and health disparities, low-income communities and communities of color are especially vulnerable to PFOA, PFOS and broader PFAS exposure, although few studies have been conducted to characterize disparities (Johnston and Cushing, 2020). A recent report analyzing California's PFAS drinking water monitoring data revealed that PFAS pollution in California is widespread throughout the state, but more intense in communities already overburdened by multiple sources of pollution and by other factors that make them more sensitive to pollution, putting those vulnerable communities at greater risk of harm from PFAS exposure. At least 69 percent of state-identified disadvantaged communities have PFAS contamination in their public water systems. Almost a quarter of these communities face the highest levels of PFAS

contamination in the state (https://www.nrdc.org/resources/dirty-water-toxic-forever-pfas-chemicals-are-prevalent-drinking-water- environmental).

Finally, by focusing only on two chemicals, both of which are long-chain PFAS, water systems are likely to invest in treatment that will not be optimized to treat short-chain PFAS that are similarly toxic. As a result, systems will likely have to spend additional money to address these other PFAS chemicals, placing a tremendous economic burden on ratepayers and potentially limiting actions that could be taken against PFAS manufacturers to recoup treatment costs. California's limited approach is, therefore, shortsighted and fails to consider the overall health and fiscal impacts of PFAS on communities."

Response 3: In addition to the PFOA and PFOS draft PHGs, notification levels (NLs) have been developed or are in the process of being developed for most of the PFAS commonly found in drinking water in California. The PHG program at OEHHA has no authority on regulating the use of PFAS. OEHHA acknowledges the importance of considering vulnerable communities in setting MCLs and related policies but defers all relevant questions to the Water Board.

Currently, OEHHA is unable to assess PFAS as a class due to data limitations on the toxicity and kinetics of the majority of PFAS. However, OEHHA is working on developing methods to conduct risk assessments on data-poor chemicals.

Comment 4: "In conclusion, our organizations support the development of public health goals for PFOA and PFOS at 0.007 ppt and 1 ppt, respectively, and strongly encourage OEHHA to use the most health protective studies to set PHGs and assess the risk of health harms for the entire class of PFAS."

Response 4: OEHHA acknowledges the comment.

NATIONAL ASSOCIATION FOR SURFACE FINISHING

General Comments: "Overall, we are concerned that the draft PHGs are not based on sound science or best risk assessment practices. OEHHA's draft PHGs contain overly conservative misrepresentations of the PFOA/PFOS-related science, resulting in proposed PHGs that are not consistent with the available science and best standards of practice. Our detailed and specific comments are provided below."

Response: Specific comments provided by this commenter are identical to comments provided by the California Association of Sanitation Agencies (CASA), thus the reader if referred above to comments from CASA and OEHHA's responses to them.

ORANGE COUNTY WATER DISTRICT

General Comments: "The Orange County Water District (OCWD) appreciates the opportunity to provide comments to the Office of Environmental Health Hazard Assessment (OEHHA) on its proposed draft Public Health Goals (PHGs) for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonic Acid (PFOS) in drinking water and the associated draft technical support document released on July 22, 2021. OCWD manages the Orange County Groundwater Basin, which typically provides more than 75% of the local water supply for 2.4 million residents. Ensuring the safety of drinking water supplies is a high priority for OCWD and the public water systems it serves. PFOA and PFOS have had a significant impact on local groundwater supplies; more than 60 public water system wells in the OCWD service have been taken offline following the Division of Drinking Water's (DDW) issuance of Notification and Response Levels, which are underpinned by earlier recommendations from OEHHA.

OCWD supports OEHHA's development of PHGs for PFOA and PFOS as a required initial step before DDW can begin its effort to establish enforceable drinking water maximum contaminant levels (MCLs) for both chemicals. Please find attached with this letter a short memorandum from Intertox, a toxicological consulting firm we have retained to assist us with our review and understanding of the draft PHGs and the associated draft technical support document. The memo contains a few questions and requests for clarification. OCWD believes that meaningful responses to these questions by OEHHA will enhance public understanding of the PHGs as well as help demonstrate that the risk assessment meets the state's statutory requirements for the development of PHGs under the California Health and Safety Code §116365 subdivision (c)(1).

Development of the PHGs for PFOA and PFOS is a welcome step towards the state's adoption of enforceable MCLs. OCWD appreciates OEHHA's consideration of these comments and looks forward to its responses."

Response: OEHHA acknowledges the comment.

Comment 1: "OEHHA presents a further analysis of the data presented in Shearer et al. (2021) and Vieira et al. (2013). These studies both present Odds Ratios (OR) for Renal Cell Carcinoma (RCC). OEHHA uses these ORs as the basis of a linear regression to derive Cancer Slope Factors (CSF) for each study which it then averages.

a. Beyond utilizing the findings from Shearer et al. (2021) and Vieira et al. (2013) publications, did OEHHA obtain and analyze the underlying raw data?

b. What was OEHHA's methodology for evaluating the appropriateness of utilizing these studies, which are based on ORs, to develop a CSF?

c. What was the basis for averaging CSFs from measured serum data and modeled serum data?"

Response 1: OEHHA did not obtain the raw data from the Shearer et al. (2021) and Vieira et al. (2013) studies. Both studies were of high quality and both publications provided sufficient information to assess the dose-response relationship between PFOA and kidney cancer. Because of this, OEHHA concluded that the raw data were not needed, and that not having these data was unlikely to lead to major bias or errors. As an aside, it should also be noted that privacy concerns could limit the ability to obtain these data. OEHHA's methodology for evaluating the Shearer et al. (2021) and Vieira et al. (2013) studies is now provided in Section 2.2.2 of the PHG document. Both studies were used because both were of high quality and it was judged that one was not necessarily more sensitive than the other. This is discussed in further detail in Section 6.2.1 of the draft PHG document.

Comment 2: "Does OEHHA have plans to evaluate the recent study by Bartell and Vieira (2021)?"

Response 2: In response to this comment, the Bartell and Vieira (2021) meta-analysis is now mentioned in the Section 5.7.1 (*PFOA, Testicular cancer)* of the draft PHG document. Further discussion of this paper is also given in the response to Comment 3 from Dr. DeWitt.

Comment 3: "Could OEHHA estimate the serum values that would correspond to the draft PHG for PFOA to compare to the serum values presented in Shearer et al. (2021) and Vieira et al. (2013) studies?"

Response 3: PHGs are expressed as drinking water concentrations because values in that format are the most useful for California water suppliers and their customers. OEHHA has not expressed these values in terms of a serum concentration because the advantages of doing so are not clear.

PFAS REGULATORY COALTION[10]

General Comment: "In the comments below, the Coalition discusses some of the challenges that the State faces in attempting to promulgate enforceable regulations, as well as some of the challenges that Coalition members face if states promulgate standards that vary from any existing or future federal standards. The Coalition appreciates the State's desire to establish health-based goals that will inform future regulation, but urges California and other states to work with the federal government to develop a consensus on the leading data relating to the human health effects of PFOA and PFOS in order to promote a cohesive national strategy to help ensure national uniformity. A patchwork set of state-specific goals and standards that vary widely would likely cause significantly more confusion and overwhelming challenges for Coalition members that operate in multiple states or nationwide."

Response: The PHG program works within the framework of the Calderon-Sher Safe Drinking Water Act of 1996, which requires OEHHA to prepare risk assessments for chemicals for which the Water Board proposes primary drinking water standards. It is outside the scope of the PHG development process to develop consensus with other states or at the federal level.

Comment 1: "The term 'PFAS' refers to a group of man-made chemicals that include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), GenX, and other fluorinated compounds. The most prevalent and available science regarding the incidence and potential health effects of PFAS is based on PFOA and PFOS, two compounds that are no longer manufactured in the United States due to voluntary phase outs over a decade ago. For replacement chemicals, industry has begun using shorter-chain PFAS that have different physical, chemical, and toxicological properties from long-chain PFOA and PFOS. The scientific understanding of how PFAS impact humans and the environment is still developing and, for thousands of PFAS compounds, much remains unknown. From a toxicological perspective, regulatory agencies must have adequate science for determining health-based values before promulgating individual-compound standards, limits, and related regulations.

Toxicologists, whether they work for various state agencies, USEPA, international standards-setting organizations, academia, or in private practice, have not yet established specific methodologies, resources, or even agreed on which of the hundreds of studies of PFAS compounds are the appropriate or critical studies that must or should support appropriate health-based values or regulatory standards. Different methodologies, levels of experience, procedural prerequisites to standards-setting, and even local political pressures are leading to consideration of very different standards in various states and at USEPA. The Coalition urges states to work with one another, and with USEPA, to continue advancing science and methodologies to inform

[10] Comment coordinators are Fredric Andes, Jeffrey Longsworth, and Tammy Helminski of Barnes & Thornburg LLP.

and encourage a more uniform approach to federal and state development of health-based PFAS guidelines and standards."

Response 1: US EPA's recently released proposed approaches for the derivation of Maximum Contaminant Level Goals (MCLGs) for PFOA and PFOS are fairly similar to those used for the proposed PHGs, and the health-based values are more conservative (US EPA, 2021a, 2021b). It appears that a reasonably uniform approach is in the process of being adopted by federal and state agencies. However, it is worth noting that PHGs are not required to conform to federal or state assessments and can rely on OEHHA's own analyses, and risk assessment and peer-reviewed guidelines.

Comment 2: "USEPA issued 'Interim Recommendations for Addressing Groundwater Contaminated with PFOA and PFOS' in December 2019 [US EPA, 2019a]. Those recommendations provide clear and consistent guidance for federal cleanup sites being evaluated and addressed under federal programs, including the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). The screening levels recommended for such cleanups are risk-based values that are used to determine if levels of contamination may warrant further investigation at a site. The recommendations are intended to be used as guidance for states to evaluate state cleanup and corrective action sites. The interim guidance recommends in relevant part:

- Using a screening level of 40 parts per trillion (ppt) to determine if either PFOA, or PFOS, or both, are present at a site and may warrant further attention.

- Using USEPA's PFOA and PFOS Lifetime Drinking Water Health Advisory level of 70 ppt as the preliminary remediation goal (PRG) for contaminated groundwater that is a current or potential source of drinking water, where no state or tribal MCL or other applicable or relevant and appropriate requirements (ARARs) are available or sufficiently protective.

In addition, USEPA is focusing significant resources on developing appropriate regulatory mechanisms specific to various PFAS compounds. For example, USEPA just issued the PFAS Strategic Roadmap: EPA's Commitments to Action 2021-2024 (Roadmap), which provides a multi-media, multi-program, national research and risk communication plan to address emerging PFAS challenges [US EPA, 2021c]. Part of USEPA's Roadmap involves expanding the scientific foundation for understanding and managing risk from PFAS, including researching improved detection and measurement methods, generating additional information about PFAS presence in the environment, improving the understanding of effective treatment and remediation methods, and developing more information regarding the potential toxicity of a broader set of PFAS. In turn, USEPA expects that this information will help states and others better manage PFAS risks. The Roadmap is an outgrowth of the PFAS Action Council established by Administrator Regan on April 27, 2021 [US EPA, 2021d]. In addition, in October 2021, USEPA published its PFAS Strategic Roadmap: EPA Commitments to Action 2021-

2042, which proposes, among other actions, an aggressive timeline for establishing a primary drinking water regulation for PFOA and PFOS.

In the Roadmap, USEPA reports that it will propose drinking National Primary Drinking Water Regulations (NPDWRs) for PFOA and PFOS in the Fall of 2022. USEPA anticipates a final regulation in the Fall of 2023. Further, in the Roadmap USEPA says it will continue to analyze whether further revisions to the NPDWRs can improve public health protection.

While we recognize that not all states and stakeholders can agree on specific priorities or approaches to PFAS regulations, USEPA and Congress are leading important national initiatives that states should support through their contribution of expertise, resources, and efforts as the United States works to respond to PFAS exposure risks. Indeed, a patchwork of 50 different state solutions is unworkable and contrary to how the U.S. has previously addressed similar emerging-contaminant issues. While some limited variation may be expected and appropriate, the highly variable regulatory health advisories, action levels, and numeric standards currently being developed or under consideration across the country create unnecessary confusion and complexity for the public and the regulated community.

The Coalition recognizes that states have elected to utilize different methods and processes for communicating risks to their populations. However, standards-setting must reflect more national and uniform collaboration and cohesion. We must work to avoid the undesirable solution of 50 separate state rules. With this in mind, we urge the states to work closely with USEPA to establish science-based and peer-reviewed federal goals and standards that serve as the basis for comparable state goals and standards. Such an approach is consistent with how USEPA and the states have addressed environmental and human health risks since the creation of USEPA."

Response 2: See response to General Comment above. Also note that once US EPA establishes MCLs for PFOA and PFOS, states must either adopt those MCLs or, if they have primacy, they may adopt MCLs that are no less stringent than those promulgated by US EPA.[11]

Comment 3: "The Coalition appreciates OEHHA's efforts to identify and utilize human studies to develop PHGs. However, the confounding factors were not well-controlled resulting in proposed PHGs that do not reflect actual health risks. For example, the Shearer, et al. study, which OEHHA relied on to develop a proposed PHG for PFOA, evaluated kidney cancer in human populations. Kidney cancer is a disease that often develops as humans age. Yet, the study's youngest participant was 55 years old. The study does not reflect the age of the general population and fails to adequately correct for age to account for the fact that kidney cancers often develop, independent of any PFOA exposure, in the older-aged population studied. The study attempts to correct for

[11] See Drinking Water Requirements for States and Public Water Systems at https://www.epa.gov/dwreginfo/primacy-enforcement-responsibility-public-water-systems

age, but because such limited data exists regarding a younger-aged population, the data cannot be accurately corrected. Because of the failure to properly account for the age and natural occurrence of kidney cancer in the population studied, the study fails to show that exposure to PFOA is associated with cancer.

By comparison, the Raleigh, et al. study that OEHHA declined to rely on in developing the proposed PHGs evaluated a younger population that is more representative of the general population. The Coalition disagrees with OEHHA's decision to disregard the Raleigh, et al. study in favor of the Shearer, et al. study, which is less representative of the age of the general population.

Additionally, the conclusions regarding the dose-response relationship in the Shearer, et al. study are flawed. The study evaluated four exposure categories with an increasingly high dose. The odds ratio actually decreased from the lowest to intermediate exposure category, and the odds ratio did not increase until the highest exposure category. The data suggests that the higher odds ratio for highest exposure group was an outlier. Absent this outlier with the highest PFOA exposure—an exposure level that would be extremely uncommon in the general population—there is no relationship between exposure and incidence of disease. In fact, absent the outlier, there appears to be an inverse relationship. Given these limitations, the Coalition disagrees that the Shearer, et al. study can be used to show that PFOA exposure correlates to cancer and supports the proposed PHG values.

Finally, in order to develop PHGs, cancer toxicity values must be established. OEHHA used only epidemiological studies for PFOA, which are less controlled than dose-response animal studies, and their sole use may introduce uncertainty into OEHHA's PFOA oral cancer slope factor [0.0026 (ng/kg-d)-1], despite attempts by the researchers to de-convolute other, non-PFOA cancer-causing factors from the data. We note that USEPA has not yet established a cancer toxicity value for PFOA."

Response 3: The Shearer et al. (2021) study matched and adjusted for age, so it's difficult to see how "confounding" by age would be a major issue in this study. Please see response to Comment 6 from Dr. Jamie DeWitt above. In addition, the study presented its findings as estimates of relative risks, not absolute risks. While absolute risks are likely to change as the study participants age, OEHHA could find no evidence that age-adjusted relative risks would do the same. Finally, the HPC calculations performed by OEHHA use the lifetime risk of kidney cancer. This value incorporates the risk of kidney cancer at all ages, not just in those younger than age 55. Overall, based on all of these factors, concerns about confounding by age are unwarranted.

While the odds ratio in Shearer et al. (2021) decreased from the second to the third highest exposure category, both odds ratios were above 1.0. As such, both indicated an increased risk of PFOA-related RCC. In addition, the confidence intervals of both of these odds ratios are wide enough that a true monotonic dose-response relationship cannot be ruled out.

The odds ratio in the highest exposure category of Shearer et al. (2021) was based on 206 participants, over 31% of all of the participants in the study. Given this high percentage, it is difficult to see how this odds ratio could be considered an "outlier." In addition, the odds ratio for the continuous analysis involved all 648 participants in the study, and it was also elevated (OR = 1.71; 95% CI, 1.23-2.37). This result is also consistent with a strong association between PFOA and RCC and certainly could not be considered an outlying value.

As extensively detailed in the draft PHG document, OEHHA thoroughly evaluated the existing research on PFOA and concluded that the human epidemiologic studies by Shearer et al. (2021) and Vieira et al. (2013) are of high quality and are appropriate for establishing the PFOA cancer HPC and the PHG.

Comment 4: "The human studies relied on to establish the proposed PHG for PFOS had an extremely high number of highly exposed individuals. It is unclear whether this exposure was continuous, but it is unlikely that a lower exposure would have had the same adverse effects. The Coalition does not agree that the studies involving such extremely high exposures provide a good reference for the development of PHGs.

OEHHA also used data from studies on lab mice and rats to inform the proposed PHGs. Again, the Coalition disagrees that such studies are reliable and appropriate for use to determine adverse health effects of PFAS exposure in humans. Mice and rats have biological differences that make them more sensitive than humans to PFAS exposure. Accordingly, the Coalition does not believe that the incidence of tumors observed in the rat and mice lab studies are relevant or instructive for the purpose of developing health-based values, like the proposed PHGs.

Further, the PFOS cancer slope factor was not derived using epidemiological studies due to the small size of such available studies. The PFOS cancer slope factor 0.000015 $(ng/kg\text{-}d)^{-1}$ was derived using only animal dose-response studies, specifically only one rat dose-response study where male rats developed liver and pancreatic tumors after ingesting PFOS for two years (Butenhoff et al., 2012a). Similar to PFOA, USEPA has not yet established a cancer toxicity value for PFOS."

Response 4: The purpose of dose-response analysis is to use data at higher exposures/doses to establish a lower dose that is not expected to pose significant risk to health. Thus, it is normal to rely on studies that observe a wider range of exposures than those observed in the target population. The continuity of response between the high and low doses is independently analyzed using modified Bradford-Hill criteria and mechanistic information, providing necessary support for extrapolation to low dose.

The animal tumors observed in the Butenhoff et al. (2012a) study are analyzed in great detail in section 5.7.3 of the draft PHG document. The commenter disagrees with the conclusions of this analysis but does not provide any additional basis for a reconsideration. It is common practice in risk assessment to base cancer assessments on animal data in the absence of human studies of sufficient quality.

Comment 5: "OEHHA's drinking water ingestion rate of 0.053 L/kg-d (equivalent to 3.71 L/day for a 70 kg adult) is notably higher than USEPA's 2014 default drinking water ingestion rates of 2 L/day for an adult and 1 L/day for a child. OEHHA's 3.71 L/day ingestion rate is not new, as it was established in 2012. Although this greater ingestion rate may be defensible given the hot summer climate in much of California, it is directly proportional to the PHG, such that the increased ingestion rate may result in an overly conservative drinking water standard for some populations and geographies, and will almost certainly result in a different PHG than would be established by EPA, all other input values being equal. This again underscores the importance of OEHHA working with the EPA towards the eventual development of consistent national standards."

Response 5: US EPA's 2019 *Update for Chapter 3 of the Exposure Factors Handbook* provides an updated drinking water rate of 2.97 L/day for all ages, consumers only (US EPA, 2019b). The factors behind the differences between the OEHHA and US EPA methodology in deriving drinking water rates are discussed in OEHHA (2012). Further consideration by OEHHA, discussed in detail in Appendix 3 of the draft PHG document, reinforces the 2012 drinking water intake rate and supports its use in PHG development.

Comment 6: "The Coalition understands that PHGs are not regulatory requirements and are based solely on the protection of public health without regard to technical feasibility, costs, or other non-health-based factors. These PHGs, however, will ultimately inform the State's drinking water standards, which must be as close to the PHGs as is economically and technically feasible. The proposed PHGs, especially for PFOA, are so far below current laboratory detection limits that it is unclear how any technically feasible and affordable drinking water standard could be based on or rationally related to the proposed PHGs. As such, the Coalition questions whether it is appropriate to establish PHGs that are so far below any value that would be technically feasible or affordable as an enforceable regulatory standard. In addition to developing and reconsidering the data relied on to support the proposed PHGs, the Coalition urges the State to use its resources to support the development of national testing, treatment, and disposal technologies."

Response 6: The matter of the PHGs being below laboratory detection limits will be considered under technological feasibility as the MCLs are developed. By law, PHGs are based exclusively on public health considerations. OEHHA does not have authority over drinking water management or PFAS treatment and disposal. Please see response to Comment 1 from the US Department of Navy above.

SAN GABRIEL VALLEY WATER ASSOCIATION

Comment: "I am writing on behalf of the San Gabriel Valley Water Association (SGVWA) with comments related to the Office of Environmental Health Hazard Assessment's (OEHHA) release of public health goals (PHG) that also impacts notification levels for PFOS and PFOA. The SGVWA's 60 members provide drinking water to 2 million residents in 31 cities through special districts, municipal utilities, investor-owned utilities, and not-for- profit mutual water companies. Our member water suppliers are deeply committed to ensuring equitable access to water that is safe for all and we feel that the proposed PHG levels present complications for some water systems statewide. The SGVWA is proposing that you address the flawed regulatory framework leading to development of the PHG and RL for PFOS and PFOA. The SGVWA has a number of purveyors with PFOS and PFOA levels exceeding current response levels (RL). OEHHA's responsibility is to set PHGs using the most up to date scientific research. In so doing, OEHHA is supposed to allow for consideration of technical research with the aim of setting a PHG reflected by the best available science. The State Water Resources Control Board (SWRCB) must set a maximum contaminant level (MCL) enforceable standard as close to the final OEHHA PHG as possible.

In practice, passage of AB 756 (C. Garcia) leaves water suppliers with no option but to treat response levels set by OEHHA as enforceable standards, as would otherwise only be the case for MCLs. The current ambiguity between a protective precautionary response level (RL) and enforceable standards (MCL) has created impacts for water suppliers and threatens public confidence in the drinking water supply. In fact, the final PHGs themselves will be treated as enforceable standards by some state agencies. This negatively affects public perception, and causes confusion when applied by others as demonstrated by the following examples:

The California Public Utilities Commission (CPUC) is not permitting investor-owned utilities to recover costs for PFOS and PFOA treatment because a response level is not an enforceable standard. Simultaneously, the Division of Drinking Water (DDW) under the SWRCB has refused to approve operating permits for some new water treatment systems if a supplier does not include treatment for PFOS and PFOA in exceedance of the RL.

The contradicting approaches by the CPUC and DDW contribute to public alarm when water systems can not immediately afford a treatment system for PFOS and PFOA. Residents in turn exhibit a distrust of tap water in favor of less regulated bottled and vending machine water. Studies demonstrate that about 40% of bottled water and 100% of vending machine water comes from domestic water supplies, including those with levels of PFOS and PFOA exceeding RLs set by OEHHA. According to studies by the Natural Resources Defense Council (NRDC), reliance on bottled water purchased at supermarkets and poorly maintained vending machines in some communities can lead to dental decay and gastrointestinal ailments.

To protect public health, we would like OEHHA to consider the combined health impacts of constituents of concern, as well as the negative impacts of California's self-defeating regulatory framework and the trade-offs in erosion of public confidence. It is essential that we protect the public by viewing PFOS and PFOA as part of the larger overall challenge created by a flawed regulatory framework as much as water quality monitoring and treatment.

The SGVWA acknowledges that PFOS and PFOA may be a health concern. We believe that the health impacts should be properly addressed. However, we must avoid at all costs undermining public confidence by creating a flawed regulatory framework."

Response: OEHHA acknowledges the comment. OEHHA has no authority over setting regulatory standards, reporting requirements, subsidizing water system infrastructure or legislative authority. OEHHA defers related concerns to the responsible state agencies.

SILENT SPRING INSTITUTE

General Comment: "We support OEHHA's rigorous analysis of cutting-edge science and the use of toxicological data to determine the public health goals (PHGs) for lifetime exposure to PFOA or PFOS. We recommend the approval of the more protective PHGs based off of cancer risks: 0.007 parts per trillion (ppt) for PFOA based on kidney cancer in humans and 1 ppt for PFOS based on liver and pancreatic tumors in animal studies. We also recommend that OEHHA extends the PHGs beyond PFOA and PFOS and adopt a class-based approach to regulation that assumes other PFAS are similarly toxic unless you have data to the contrary."

Response: OEHHA acknowledges the comment. Regarding a class-based approach, see Response 2 below.

Comment 1: "We found the overall scientific approach to calculating the PHGs for PFOA and PFOS to be thorough and well-reasoned. The PHGs of 0.007 ppt for PFOA and 1 ppt for PFOS are appropriate based on the weight of evidence and calculations for protection against cancer, and they should be protective against non-cancer toxic effects as well.

We appreciated the discussion of PFOA and PFOS effects on hormone levels and on the mammary gland. However, we noted that the discussion of reproductive and developmental toxicity failed to include several epidemiological and animal studies demonstrating impaired ability to breastfeed in mothers and delayed breast development in girls. For example, several well-powered epidemiological studies have documented associations between serum PFAS (including PFOA and PFOS) and reduced duration of breastfeeding [Fei et al., 2010; Timmermann et al., 2022; Timmermann et al., 2017]. While early termination of breastfeeding can be related to several sociocultural factors, the most common reasons are concerns about insufficient milk supply, milk quality, and pain [Ahluwalia et al., 2005; Gianni et al., 2019; Lechosa-Muñiz et al., 2021; Stuebe et al., 2014], which are all related to hormonal imbalances. The lowest serum concentrations observed to have a significant odds ratio (OR) for reduced breastfeeding time was 1 ng/mL PFOA and 10 ng/mL PFOS [Ahluwalia et al., 2005]. These are substantially lower than the NOAEC level of 9.8 ng/mL PFOA for elevated ALT and LOAEC of 16.4 ng/mL PFOS for elevated cholesterol cited in the OEHHA draft PHG document. The potential for PFAS chemicals to impair breastfeeding is supported by studies in rodents showing that PFOA exposure during pregnancy impairs lactation through reduced epithelial differentiation and altered milk protein production [White et al., 2007; White et al., 2011], resulting in dose-dependent increases in pup morbidity but not maternal toxicity [Lau et al., 2006; White et al., 2007].

Multiple studies in rodents have also demonstrated that prenatal exposure to PFOA delays mammary gland development [Macon et al., 2011; Tucker et al., 2015; White et al., 2007; White et al., 2011]. A dose of 0.01 mg PFOA/kd/day in CD-1 mouse dams for under 40% of pregnancy (gestation day 10-17) was capable of inducing significant delays in ductal elongation and branching and terminal end bud formation in pups, with

effects that persisted into adulthood [Lopez-Espinosa et al., 2011]. The PFOA-induced delays in mammary gland development and lactation-related defects were evident across three generations of mice [White et al., 2011], underscoring the importance of addressing this effect in public health guidance documents to prevent additive or synergistic effects of continued PFAS exposure across generations of humans.

As additional epidemiological evidence of how PFAS may impact pubertal development in girls, perinatal exposure to PFOA has been associated with delays in menstruation (> 4.4 – 19.8 ng/mL PFOA in serum) [Kristensen et al., 2013] and breast development [Kale et al., 2015; Pinney et al., 2014]; while peripubertal serum levels of PFOA (> 11.4 ng/mL) and PFOS (> 23 ng/mL) were both associated with delayed menstruation [Lopez-Espinosa et al., 2011]. Such epidemiological evidence illustrates that more women-relevant endpoints should be considered in the formation of the non-cancer PHGs for PFOS and PFOA, and if they were the PHGs would likely be lower than the proposed 2ppt for PFOS and 3ppt for PFOA.

In summary, we found that adverse non-cancer effects on the mammary gland are evident for impaired lactation at 1 ng/mL PFOA and 10 ng/mL PFOS, which are lower than the NOAEC of 9.8 ng/mL PFOA for elevated ALT and LOAEC of 16.4 ng/mL PFOS for elevated cholesterol used by OEHHA. Inclusion of effects on lactation/breastfeeding would have yielded more protective non-cancer-based guidelines. However, the final PHG of 0.007 ppt for PFOA and 1 ppt for PFOS (selected based on cancer endpoints) should be protective against adverse effects on the mammary gland as well. We commend OEHHA for their careful and health protective approach."

Response 1: OEHHA acknowledges the comment.

Comment 2: "As we discuss below, since the public is exposed to many additional PFAS chemicals that have similar toxic effects, using a class-based approach that assumes all PFAS have similar toxicity as PFOA and PFOS seems appropriate. This class-based approach is more likely to be protective against both cancer and non-cancer toxic effects for the vast mixture of PFAS in the environment, including many that have yet to be rigorously evaluated in epidemiological and toxicological studies."

"We urge OEHHA to develop a class-based PHG for all PFAS and recommend to the State Water Resources Control Board that they set class-based MCLs for PFAS to provide more holistic public health protection.

The EPA has identified over 9,000 compounds classified as PFAS [https://comptox.epa.gov/dashboard/chemical_lists/pfasmaster], and many have been associated with industrial uses and consumer products [Glüge et al., 2020]. This class of chemicals is associated with a wide range of adverse health outcomes, including cancer, immunotoxicity, reproductive toxicity, developmental effects on the mammary gland, neurotoxicity, and thyroid, liver, and kidney effects [ATSDR, 2021]. However, given the size of this chemical family, conducting human health risk assessments for each individual PFAS compound is not possible. Despite the high diversity of the class,

PFAS are all alike in that they contain perfluoroalkyl moieties that are extremely resistant to environmental and metabolic degradation, and this high persistence means that their continual release will result in accumulating environmental concentrations and increasing probabilities of the occurrence of irreversible harms [Cousins et al., 2020]. Due to the toxic, mobile, persistent, ubiquitous and diverse nature of these chemicals, it is well recognized that effective regulation of PFAS will need to use a class-based approach that assumes similar toxicity across the class, unless there is empirical information to the contrary.

The American Public Health Association [APHA, 2016] and a number of expert scientists including Dr. Linda Birnbaum, former head of the National Institute for Environmental Health Sciences, have recommended approaching PFAS as a class based on their shared chemical properties and have urged reducing overall use of PFAS [Birnbaum, 2019; Birnbaum and Grandjean, 2015; Blum et al., 2015; Kwiatkowski et al., 2020]. Past examples (such as flame retardants [NASEM, 2019] and CFCs) have shown that a one-chemical-at-a-time approach has not been effective at protecting public health and the global environment. The OECD already recognizes PFAS as a class [OECD, 2021], and in 2019 the European Union recommended an action plan to eliminate all non-essential uses of PFAS as a class [Council of the European Union, 2019], indicating regulatory agencies are already moving in this direction.

In fact, California's own Department of Toxic Substances Control is already regulating PFAS as a chemical class, citing this approach as 'logical' and 'necessary' given that all PFAS, and their degradation, reaction, or metabolism products, display common hazardous traits [Bălan et al., 2021]. Silent Spring's own research on PFAS exposures to firefighters and office workers in California's Bay Area [Trowbridge et al., 2020] found that 70% of study participants had detectable levels of 7 out of the tested 12 target PFAS analytes, and 100% have detectable levels of 4 PFAS—pointing to the fact that simply regulating 2 individual PFAS, PFOS and PFOA, is not enough.

In fact, other regulatory agencies in California have already recognized that PFOA and PFOS are not the only chemicals of concern in California's drinking water. While California's State Water Resources Control Board set notification levels for PFOA and PFOS in drinking water in 2018, they recently added notification levels for PFBS in January 2021, and are looking into developing notification levels for PFHxS, PFHxA, PFHpA, PFNA, PFDA, and ADONA.

Regarding drinking water particularly, recent research has shown that less than half the total organic fluorine measured in treated drinking water were accounted for by the sum of individually identified PFAS [Hu et al., 2019]. This indicates that there are likely many more PFAS in the water than would be identified by a targeted analysis, and points to the need to monitor, report, and regulate PFAS as a class. Therefore, it is critical that OEHHA sets a public health goal (PHG) for PFAS as a class.

As a initial step towards regulating PFAS as a class, the state could measure total PFAS in various environmental and biological media on a regular basis to assess the

abundance of non-regulated PFAS. Meanwhile, other regulatory bodies are proposing innovative solutions to the challenges of regulating PFAS as a group in drinking water. Recently, the EU proposed two drinking water guidelines based on differing groupings of PFAS compounds: 100 ng/L for the sum of 20 PFAS compounds (perfluorocarboxylic acids and perfluorosulfonic acids), and 500 ng/L for the sum of all total PFAS. These values will apply once technical guidelines for monitoring these parameters are developed in accordance with Article 13(7). Member States may then decide to use either one or both of the parameters. This proposal by the EU is an example of how regulating a large group of drinking water contaminants such as PFAS. We urge OEHHA to perform similar action towards creating PHGs that address PFAS in drinking water as a class."

Response 2: Complex scientific and regulatory decisions are involved in grouping PFAS for purposes of monitoring or for the development of regulatory standards. Based on several released NLs and proposed PHGs, it has become clear that PFAS demonstrate a wide range of toxicokinetic properties and toxicities that do not completely overlap. As a result, NL and PHG values differ by orders of magnitude. Thus, assigning a single health-protective value to a group of PFAS could be under protective or overly conservative for most chemicals in the group. The rationale for grouping PFAS may be different for different types of exposure and in different regulatory contexts. The work on possible PFAS grouping for NL and PHG development purposes is ongoing at OEHHA. Since individual health values are available or will soon become available for most known PFAS of interest in drinking water in California, one can also use the hazard index approach to analyze the overall risk from the mixture of the compounds.

The potential presence of additional unidentified PFAS in drinking water is a known problem. However, it is not yet known how much of the unidentified organic fluorine fraction in drinking water constitutes unidentified PFAS, and there are no analytical techniques to identify total PFAS. The vast majority of PFAS lack toxicity data and require the development of predictive approaches. To address these challenges, OEHHA continues to work with the Water Board on identifying PFAS of emerging concern in drinking water and on developing novel approaches to health-based risk assessments.

Comment 3: "In summary, the available science supports the final OEHHA PHG of 0.007 ppt for PFOA and 1 ppt for PFOS. Exposure to highly persistent PFAS have been associated with a range of health hazards and we commend OEHHA for taking this critical step towards protecting Californians. Setting a PHG for PFAS as a class would be a more protective public health measure and is in line with the action taken by other regulatory agencies and recommendations by prominent experts in the field. We hope OEHHA will continue to work towards this goal."

Response 3: OEHHA acknowledges the comment.

WESTERN STATES PETROLEUM ASSOCIATION

Comment 1: "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]

[Footnotes]

[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."

Response 1: PHGs are health-based values that are not enforceable. The Water Board establishes MCLs based on PHGs but also takes into consideration other factors including detection limits. The commenter's concerns regarding the quality of studies used to support PFOA and PFOS PHGs are addressed below in responses to their more detailed comments.

Comment 2: "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, 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."

Response 2: These issues are addressed separately in comments below.

Comment 3: "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."

Response 3: As detailed in Section 6.2.1 of the draft PHG document, the three studies cited by the commenter, both individually and as a whole, provide a consistent and strong body evidence that PFOA causes kidney cancer.

Comment 4: "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."

Response 4: The Shearer et al. (2021) study adjusted or otherwise controlled for all of the major risk factors for kidney cancer. Multiple subgroup analyses also showed that these factors caused little to no confounding. Many of the key results in this study were statistically significant, so claims that this study was too small (or did not have enough controls) are unwarranted.

Comment 5: "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."

Response 5: No clear explanation or any evidence is presented in this comment that the use of relative risks rather than absolute risks by Shearer et al. (2021) was likely to cause major bias or errors in the HPC or PHG calculations. OEHHA was also unable to identify any evidence or rational explanation to support this claim.

Comment 6: "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."

Response 6: Please see the response to the Comment 8 by the American Chemistry Council and others above regarding outlying values and ranges. Overall, OEHHA sees no clear reasons why the issue raised in this comment would cause major bias, and the commenter has not presented any.

Comment 7: "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."

Response 7: Supplementary Figure 1 in Shearer et al. (2021) provides some information on the distribution of the exposure data in this study. As noted in the response to Comment 8 by the American Chemistry Council and others, Shearer et al. (2021) performed both continuous and categorical analyses, and a major advantage of the latter is that it reduces the potential impact of outlying values. Importantly, the results from the categorical analysis are the ones that OEHHA used to establish its proposed PHG.

Comment 8: "Based on the results from Table 2 [Shearer et al., 2021], 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."

Response 8: The relationship between PFOA and RCC was not "gone" following adjustment for other PFAS. In fact, it stayed about the same (odds ratios of 1.71 and 1.68, respectively, before and after adjustment). Importantly, conclusions based solely on p-values are inappropriate in this particular context (and in many others). Please see the response to Comment 18 by the Department of Navy.

Comment 9: "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."

Response 9: No evidence is presented by the commenter that the participants of Shearer et al. (2021) were at a higher risk of cancer before the trial than the general US population. In fact, the rates of kidney cancer among the participants of this trial appeared to be similar to those in the US as a whole (see Section 6.2.1 of the draft PHG document). Finally, if the Shearer at al. (2021) participants really were at a greater risk of cancer when the trial started, as is being proposed above, this would most likely affect both the people who ended up getting cancer and those who didn't (i.e., it would affect both the cases and controls). As such, this would not cause major bias to relative risk estimates.

OEHHA agrees that information is not currently available on the possible racial and ethnic differences that may exist in PFAS carcinogenicity, and that the cancer risks of PFOA could be greater in certain races and ethnicities than those reported by the Shearer et al. (2021) and Vieira et al. (22013) studies. Currently, however, the research needed to quantify these potential differences, if they exist, has not been done.

Comment 10: "There is only a 1:1 ratio between cases and controls [in Shearer et al. (2021)], 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."

Response 10: No justification is provided in this comment for why a 1:4 ratio of cases and controls would be "ideal," and there is no underlying basic epidemiologic principle supporting this contention. The key reason to increase the control to case ratio beyond 1:1 would be to increase statistical power. However, as noted in the response to Comment 4 from this commenter, a lack of statistical power was not a major limitation of this study.

Comment 11: "The study by Shearer *et al*. (2021), therefore, cannot be used to reliably quantify the attributed risk of RCC to a PFAS-exposed population."

Response 11: OEHHA disagrees. Please see the responses to the specific comments above as well as the thorough discussion presented in Section 6.2.1 of the draft PHG document.

Comment 12: "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 Ceriotti *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."

Response 12: As noted in the Section 6.1.1 (*Summary: PFOA PODs*) of the draft PHG document, OEHHA did not use the mean ALT values from Gallo et al. (2012) as the basis of its HPC calculation (Gallo et al., 2012). Rather, OEHHA used the results for having an elevated ALT. As noted in the draft PHG document, the cut-off points used to define these elevations were based on clinical guidelines, and ALT levels above these cut-off points have been linked to major increases in both morbidity and mortality.

Comment 13: "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 (US EPA, 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."

Response 13: OEHHA did not use a combined UF of 300 for the proposed PFOA and PFOS HPCs. The combined UF for calculation of the noncancer ADD was √10 for PFOA and 10 for PFOS. For more details on OEHHA's UFs in the noncancer assessment, please see response to Comment 4 from the US Department of Navy above.

Comment 14: "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."

Response 14: The commenter states there were critical flaws in the Butenhoff et al. (2012) study but does not elaborate further. While OEHHA used a linear extrapolation to low dose for determining the CSF, the dose-response of the bioassay itself does not necessarily have to be linear, as the commenter suggests. Both liver and pancreatic tumors in Butenhoff et al. (2012a) were significant in trend tests, indicating the presence of a dose-response. In developing the PFOS CSF, OEHHA followed a standard practice similar to that of US EPA and other regulatory agencies. Key uncertainties pertaining to this assessment are summarized in Chapter 8. Additionally, PFOS was recently listed under Proposition 65 as a carcinogen, following an evaluation by the State's Carcinogen Identification Committee using similar evidence provided in the draft PHG. Please also see response to Comment 3 from the California Association of Sanitation Agencies above.

Comment 15: "The 2021 OEHHA report relied almost solely on an article by Butenhoff, *et al*. (2012) to assert the potential oncogenic effects of PFOS."

Response 15: Correct, OEHHA used Butenhoff et al. (2012a) as the main study for evaluating PFOS as a carcinogen. Although a single study, tumors were reported for both sexes and in multiple tissues. OEHHA also used mechanistic studies and key characteristics of carcinogens in its consideration of PFOS as a carcinogen.

Comment 16: "The Butenhoff, *et al*. paper did not report any kind of dose-response for hepatocellular adenomas in male rats with PFOS exposure. 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.

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."

Response 16: The statistically significant results of the trend test of incidences of hepatic and pancreatic tumors in Butenhoff et al. (2012a) in Table 5.7.7 and 5.7.8 of the draft PHG document indicate the presence of significant dose-response trends in this bioassay. The tumor incidence data do not have to be linear in order to perform a linear low dose extrapolation. The inconsistencies that the comment points out are not valid.

Animal bioassays are conducted at doses (and serum concentrations) that are much higher than those observed in humans because they detect tumors at much higher incidences than would be expected to occur in the human population. This is the basis of linear extrapolation to a low dose. Please also see response to Comment 3 from the California Association of Sanitation Agencies above.

Comment 17: "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."

"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."

Response 17: In calculating a human CSF from an animal CSF, body weight scaling ratio to the one eighth power was applied to adjust for toxicodynamic differences only. Toxicokinetic differences were adjusted separately, through use of the clearance factor.

The concerns that the comment lists apply to toxicokinetic and not to toxicodynamic adjustments. In the PFOS CSF calculation, OEHHA did not use body weight scaling to account for toxicokinetic differences and therefore, concerns expressed in the comment to would not apply to this calculation.

Comment 18: "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."

Response 18: Analysis of PFOS mechanistic data for carcinogenicity indicates a carcinogenicity concern. Please see response to Comment 3 from the California Association of Sanitation Agencies above. Supportive human evidence is not required for carcinogens with a genotoxic MOA (or for which a genotoxic MOA cannot be excluded) such as PFOS.

Comment 19: "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."

Response 19: This comment is addressed in detail below.

Comment 20: "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."

Response 20: OEHHA presented the numbers cited by the commenter simply as a starting point for much more detailed discussions and analyses of causal inference. The commenter simply presents the number counts and has not provided any other evaluation of causality. As noted in the draft PHG document, a number of high quality studies have reported associations between PFOS and elevated TC and LDL levels, and evaluations of bias, confounding, and causality all show that these results represent real effects (please see Section 5.3, Section 6.1.2, and Table A7.8 of the draft PHG document).

Comment 21: "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."

Response 21: The implication that cross-sectional studies can never be used to assess causality is unsupportable. In some instances, cross-sectional studies can be used to assess causality and in some instances, they cannot. Each study and each situation should be evaluated on its own merits. This is what OEHHA has done, and based on these evaluations OEHHA has concluded that the cross-sectional design used by Steenland et al. (2009) was a valid design for assessing the risks of PFOS and TC (Steenland et al., 2009). Further discussion of this issue is provided in Section 6.1.2 (*Summary: PFOA PODs*) of the draft PHG document.

Some studies may not have addressed some of the Hill criteria, but all of these criteria have been addressed in at least one study (and usually in many more). Most importantly though, OEHHA has addressed them all. It is important to note that in his seminal work on these criteria (Hill, 1965), Austin Bradford Hill wrote that none of the nine causal criteria he put forward "can be required as a *sine qua non*." As such, according to the Hill criteria, the lack of a clearly defined mechanism does not preclude a firm conclusion that a causal relationship exists.

Comment 22: "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."

Response 22: OEHHA acknowledges the comment. The draft PHG document discusses the difference in cholesterol response between humans and animals and does not use animal cholesterol findings for human health extrapolation. Please also see response to Comment 40 from 3M Company above.

Comment 23: "Lastly, the clinical relevance [of cholesterol endpoints] 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."

Response 23: The PFOS noncancer HPC is based on human data, and lower PODs from human studies compared to animal studies was one of the reasons for this choice.

Comment 24: "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 (US EPA, 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."

Response 24: OEHHA did not use a CSAF in its cancer calculations. The mechanistic evidence regarding PPARα involvement in the cancer MOA is reviewed in great detail in Section 5.7.3 of the draft PHG document. Based on all available evidence, OEHHA concluded that a PPARα-dependent MOA is unlikely to be the sole MOA, found evidence for several key characteristics, and that a genotoxic MOA cannot be excluded. In this case, the default method of CSF calculation and linear extrapolation to low dose is adopted. Please also see above response to comment 11 from the California Association of Sanitation Agencies.

Comment 25: "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."

Response 25: Bernstein, Kapraun and Schlosser (2021) is a review of existing PBPK models, not an original study. The draft PHG document reviewed existing PBPK models in Section 4.6. As detailed in the document OEHHA concluded that existing human PBPK models have clear limitations, are not sufficiently validated and likely do not provide any advantage over a simpler toxicokinetic adjustment while significantly increasing uncertainty.

Comment 26: "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."

Response 26: It is unclear exactly what the commenter means when referring to "pharmacokinetic linearity" or "non-linear dose-response relationship." Firstly, no linearity is assumed in how exposed subjects develop tumors. The observed tumor incidences (in epidemiologic or animal bioassay datasets) are analyzed with appropriate dose-response methods. The resulting functional dependence may turn out to be linear if the fit of the model to observed values is optimal. Secondly, it is well known that the dependence of serum concentration on dose is not linear for either PFOA or PFOS, complicating conversions between administered animal dose and animal serum concentration. However, no such conversion was performed in the draft PHG document, and an alternative method, such as using serum concentrations was selected instead. Lastly, once a pollutant is analyzed as a genotoxic carcinogen, then linear extrapolation to low dose is applied (for which the CSF is the slope), which is a common practice (US EPA, 2005).

In the PHG draft, OEHHA assumed a first order toxicokinetic elimination model for humans, for which the document provides justification. It is not clear if the comment's "linear approach" refers to this TK adjustment. The PHG draft document does not refer to this method using the term "linear."

ANONYMOUS AND M MCANEAR

Comment 1 (by anonymous): "Please protect all Californians and set the PHGs for PFOA, PFOS and all PFAS at 1 ppt. These are toxic chemicals that build up in out bodies and never break down in the environment. Please, take action to keep them all out of our water and make the polluters pay for the clean up."

Response 1: See response to Comment 2 from CleanEarth4Kids.org.

Comment 2 (by M. McAnear): "Please keep our water pure for future generations. We must act now and have strict laws."

Response 2: OEHHA acknowledges the comment.

RESPONSES TO COMMENTS MADE DURING THE SECOND PUBLIC COMMENT PERIOD (July 14 – August 29, 2023)

THE AMERICAN CHEMISTRY COUNCIL

Comment 1: "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). 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."

Response 1: The new publications provided by the commenter have been reviewed. Most of these are not original new research but rather are reviews of research studies that have been evaluated by OEHHA and were already included in the Public Health Goal (PHG) document. The two exceptions are Schillemans et al. (2022) and Timmermann et al. (2022). The latter wasn't cited by the commenter but is included in the meta-analysis by Zhang et al. (2022). Overall, the results of these two new studies support OEHHA's conclusions regarding PFOS and serum cholesterol and OEHHA's conclusions regarding the immune effects of PFOS and PFOA. Both studies are now included in the PHG document (Table A7.29).

OEHHA thoroughly reviewed the two epidemiologic studies on cancer (Shearer et al., 2021; Vieira et al., 2013) used to develop the PHG for PFOA and found that both used valid information on exposure (see discussion in the PHG document, Section 6.2.1). OEHHA also found that the results of these studies were not "questionable" but rather met essentially all the major criteria commonly used to evaluate causal inference. An extensive discussion of these causal inference evaluations can be found in Section 6.2.1 of the PHG document.

OEHHA did not find the human epidemiologic evidence for PFOA and cancer to be "conflicting." As discussed in Section 6.2.1 (*Criteria for causal inference*), OEHHA initially identified seven human studies of PFOA and kidney cancer, although two of these are not informative because of the ecologic nature of the study or the small number of kidney cancer cases. Of the remaining five, four were judged to be of high quality, and all four reported statistically significant associations between PFOA and kidney cancer (Barry et al., 2013; Shearer et al., 2021; Steenland and Woskie 2012; Vieira et al., 2013). The fifth study did not report clear associations but had a number of weaknesses that may have limited its ability to identify true effects (Raleigh et al. 2014). These weaknesses are described in Section 6.2.1 of the PHG document. An additional study of serum PFOA concentrations and renal cell carcinoma has recently been published (Rhee et al., 2023; see Table A7.29 of the PHG document). This study also reported findings that were consistent with the two studies OEHHA used to develop its PFOA PHG. Overall, based on its evaluations of study quality and validity, OEHHA found a consistent body of human epidemiologic evidence that PFOA causes kidney cancer.

Regarding the animal cancer bioassays, benchmark dose methodologies, and the selection of the relative source contribution, please see the responses to Comments 7-9, Comment 12, and Comments 14-16 below.

Comment 2: "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) and Vieira *et al*. (2013). 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. 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."

Response 2: The commenter does not name the study in which they feel "the potential exposure to PFOA was better characterized" but presumably this was the study by Raleigh et al. (2014). OEHHA agrees that the results of Shearer et al. (2021) and Vieira et al. (2013) were not supported by the results of Raleigh et al. (2014) but disagrees that PFOA exposure was better characterized in the latter. In fact, the methods used to assign exposure levels in Raleigh et al. (2014) had a number of potential weaknesses that may have limited the validity of this study's results. For example, much of the exposure information was based on either expert judgment, extrapolations, or PFOA concentrations in air, and not on actual internal measures of PFOA exposure (i.e., serum measurements). Additionally, PFOA exposures from drinking water were not considered, despite the high drinking water levels in the surrounding residential areas, and no validation data were provided. Based on these and other weaknesses, OEHHA finds no reason to believe that the PFOA exposures in Raleigh et al. (2014) were better characterized than those in Shearer et al. (2021) or Vieira et al. (2013).

OEHHA disagrees with the commenter's contention that "epidemiology is generally used to complement the animal data in corroborating or clarifying the carcinogenic potential of a substance." According to the US EPA guidelines cited by the commenter, "When human data of high quality and adequate statistical power are available, they are generally preferable over animal data and should be given greater weight in hazard characterization and dose-response assessment…" (US EPA 2005). OEHHA agrees with US EPA and found that human studies of high quality and adequate statistical power are available on PFOA and cancer. The data and evaluations that led to this conclusion are provided in Section 6.2.1 and Table A7.23 of the PHG document.

With regards to the commenters statement that, "the human cancer profiles are not consistent with observations of cancer in animal studies," the US EPA guidance document (US EPA, 2005) cited by the commenter states that, "Target organ concordance is not a prerequisite for evaluating the implications of animal study results for humans." This document also notes that there are "numerous examples of an agent causing different cancers in different species." OEHHA is aware that increases in renal tumors have not been seen in PFOA-exposed laboratory animals. However, cancers at other sites have been reported (see Section 5.7.2 of the PHG document). And, as described in Sections 5.7.1 and 6.2.1, and Table A7.23 of the PHG document, clear and consistent associations between PFOA and cancer have been found in several high quality human studies. As a whole, this body of research provides strong and convincing evidence that PFOA is a human carcinogen.

The commenter's statement regarding exposure uncertainty, confounding factors, and adequate sample size are discussed in the following responses.

Comment 3: "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. 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 in addition to the case-control 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)

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			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). The supplemental information provided by 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. 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 echoed by EPA 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). 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."

Response 3: Assigning quantiles based on the distribution of the exposure in controls is a common practice in epidemiology, and in the case of Shearer et al. (2021) there is no evidence that this had any adverse impacts on the dose-response trends reported in the study.

The commenter's analysis of the data in Table 1 above is based entirely on statistical significance (i.e., confidence intervals), without consideration of any of the other important factors that typically go into evaluations of causal inference. Numerous authors have warned about the serious errors that can occur when conclusions are based solely on confidence intervals or other tests of statistical significance (Altman and Bland 1995; Greenland et al., 2016; Lang et al., 1998; Leek and Peng 2015; Sterne and Davey Smith 2001; Wasserstein and Lazar 2016). The references provided here are only a small fraction of the extensive literature on this topic, and the general consensus of this literature is that it is poor epidemiologic practice to over-emphasize tests of statistical significance. In fact, Dr. John Adgate, an external scientific peer reviewer of the PHG document, also cautioned against relying too heavily on statistical significance alone in evaluating causal inference. Regardless, OEHHA did not use the data from Shearer et al. (2021) as they are presented in Table

1 above for its dose-response calculations because those findings have a major weakness (i.e., multi-colinearity). These particular results are further discussed in the PHG document (Section 6.2.1) as well as in the response to the October 2021 comments from the American Chemistry Council (Comment 6). As described in Section 6.2.1 of the PHG document, the results from Shearer et al. (2021) used by OEHHA in the PHG calculations were not only statistically significant (p=0.007), but they also met all of the other major criteria for causal inference.

The commenter suggests that the use of a single serum sample to assess exposure in Shearer et al. (2021) is a concern, but has not provided any evidence, objective or otherwise, that this caused major bias. OEHHA has evaluated this issue and found no evidence or reason to believe that the use of a single serum sample had a major impact on the validity of the results reported for this study. Please see Section 6.2.1 of the PHG document, as well as the responses to the October 2021 comments from the 3M Company (Comment 26) and the California Association of Sanitation Agencies (Comment 6) for further discussions of this issue. OEHHA agrees with the commenter that the serum PFAS concentrations in Shearer et al. (2021) reflect general population exposures. However, this is not a weakness. Rather, it is an important advantage since a major aim of the PHG is to protect the general population.

The commenter states that, “the range of [PFOA] serum levels was only slightly higher among the cancer cases compared to the controls” in the Shearer et al. (2021) study. However, comparing the ranges of exposure between cases and controls is an over simplified and commonly unhelpful method for assessing associations in cancer studies. An important reason for this is that it relies on only four data points (the upper and lower bound in cases and the upper and lower bound in controls) despite the fact that hundreds of other relevant data points are available. One could compare the median exposure levels between cases and controls, and this information was provided as a figure in the Shearer et al. (2021) supplementary file (their Supplementary Figure 1). This figure shows that the median serum PFOA level was higher in cancer cases than in controls, although the actual magnitude of this difference was not provided and is difficult to estimate given that the PFOA measurements shown were log transformed. Regardless, a simple comparison of median exposure levels is also a relatively crude way of assessing associations in environmental cancer studies since a significant amount of detail from the underlying data is lost and almost no information on overall dose-response trends is provided in this type of assessment. Fortunately, much more sophisticated and informative analyses were presented by Shearer et al. (2021) (e.g., in their Table 2, Figure 1, and Supplementary Figures 2-4), and the results of these provided strong evidence that PFOA causes human cancer.

The 95% confidence interval for the highest exposure category in Shearer et al. (2021) was 1.33 to 5.20, which does not seem unnecessarily broad as the commenter suggests. While the Shearer et al. (2021) study authors did not explain how the potential outlier described by the commenter may have impacted their results, this omission is not a fatal flaw and does not preclude the use of this study for dose-

response analysis. There are several reasons for this. For one, because the exposure variable in the continuous analysis was log-transformed, it is not clear that this single data point would have had a major impact on these results. Secondly, this outlier represents an actual person, with an actual serum PFOA concentration, and was a study participant who actually had cancer. In other words, this data point is not necessarily a mistake and therefore not necessarily an error that needs to be corrected or removed. Finally, OEHHA used the findings from the categorical analysis, not the continuous data analysis, for its dose-response assessment. One of the major advantages of using categorical data is that they are much less likely to be affected by outlying values. Based on this rationale, there is little to no reason to believe that the single data point noted by the commenter had any major impact on OEHHA's cancer slope factor calculations.

The commenter states that "a robust uncertainty or sensitivity analysis…are missing from the Shearer *et al.* publication." It should be noted that the Shearer et al. (2021) study was conducted by one of the most pre-eminent cancer research institutions in the world, and the research findings from this organization typically undergo extensive internal and external peer review prior to publication. It should also be noted that the authors used appropriate, well known, and widely accepted methods for its study design, statistical analyses, and reporting of results. Numerous statistical tests were conducted and presented in this publication, and these provide a robust picture of the statistical uncertainty associated with the study's results. A variety of sensitivity analyses were also conducted, and these provide key information for evaluating bias, confounding, and causality. Please see Table 2, Figure 1, Supplementary Table 3, and Supplementary Figures 2-4 of Shearer et al. (2021) for examples of these analyses. OEHHA is unaware of any other "equation that explains the relationship between the continuous variables" that might be needed to evaluate the quality of this study or the validity of its results. Overall, all of the critical information needed to accurately assess the dose-response relationship between PFOA and kidney cancer was provided in the Shearer et al. (2021) publication, and the methods used to conduct and report this study are all consistent with the "best practice for epidemiology."

While it may be common for nested case-control studies to have four or five controls per case, it is also common for these studies to have one control per case. A quick search of PubMed using the phrase "nested case-control study" will confirm this. The key to determining the most appropriate case to control ratio is not through the selection of some arbitrary number, but rather through calculations of statistical power and analyses of potentially useful matching factors. The 1:1 control to case ratio used by Shearer et al. (2021) allowed the researchers to match cases and controls on a number of important matching factors including age, sex, race/ethnicity, study center, and year of blood draw. The 1:1 ratio also allowed for a good level of statistical power as can be seen by the low p-values reported for many of the Shearer et al. (2021) results. Overall, OEHHA sees no practical, theoretical, or logical reason why the Shearer et al. (2021) study needed a control to case ratio greater than 1:1.

Although the 2022 US EPA Scientific Advisory Board (SAB) mentioned a few potential limitations of Shearer et al. (2021) this committee did not present a full qualitative or quantitative evaluation of these limitations or a full evaluation of causal inference (US EPA Scientific Advisory Board, 2022). For example, detailed analyses of confounding, co-linearity, or the effect of log-transformations were not provided. Most importantly though, the 2022 SAB did not describe these potential weaknesses as fatal flaws, and never recommended, either explicitly or implicitly, that the Shearer et al. (2021) study not be used for cancer slope factor calculations.

With regards to confounding, although the US EPA rated the Shearer et al. (2021) study as "deficient" on this criterion, an objective or detailed evaluation was not presented (US EPA, 2023b). For a factor to have an important confounding effect, it must meet certain criteria. These criteria are described in Section 2.2.2 of the PHG document under the heading *Confounding*. Briefly, for a factor to cause important confounding it must be related to both the exposure and the outcome being studied, and these relationships must be relatively strong (Axelson, 1978). The factor must also be prevalent enough to have a relatively broad effect. If each of these criteria are not met, then important confounding will not occur. The only potential confounder of concern noted by US EPA was socioeconomic status (SES) (US EPA, 2023b). However, no information was presented by US EPA about whether SES was strongly related to either PFOA exposure or to kidney cancer. As discussed in the response to the peer review comment by Dr. Jamie Dewitt (Comment 6), OEHHA has qualitatively and quantitatively examined this issue and found that it is highly unlikely that confounding by SES caused the positive associations between PFOA and cancer identified in Shearer et al. (2021). Based on this evaluation, OEHHA disagrees with US EPA's rating for confounding for the Shearer et al. (2021) study and concludes that this domain should have been rated as "good" rather than "deficient." With this rating, the Shearer et al. (2021) study would meet US EPA's criteria for being a "High Confidence" study (US EPA 2023c).

With regards to US EPA's evaluations of Sensitivity and Selective Reporting (i.e., "Selectivity") US EPA explicitly states that there were "no concerns" for either of these domains for the Shearer et al. (2021) study (US EPA 2023b). As noted in Section 6.2.1 of the PHG document, OEHHA agrees with this assessment.

Comment 4: "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. In their study, Vieira *et al.* identified cases of kidney and 17 other 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.

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.

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)

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

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."

Response 4: Much of the information presented in this comment has already been reviewed by OEHHA and is in the PHG document (Section 6.2.1 and Table A7.23).

With regards to the water district analyses, the commenter's focus again is only on statistical significance, and not on any of the other important aspects of assessing causality. For example, these analyses essentially assume that everyone in any given water district all have the same PFOA exposure level. However, data from this study area clearly show that this is far from true (Shin et al., 2011) . This type of poorly classified exposure data can easily cause a study to miss or underestimate true associations, and issues like this should be considered when evaluating the validity or importance of study results.

With regards to the serum concentration groupings in Vieira et al. (2013), there is no evidence or logical reason to believe that the groupings used in this study would affect the validity of this study's results, and the commenter has not provided any.

In the accompanying table, the commenter again highlights the confidence intervals that include one. However, as noted above, serious errors and misinterpretations can occur when conclusions are based solely on tests of statistical significance, and doing so is considered poor epidemiologic practice. Rather than base its conclusions solely on these statistical tests, OEHHA performed full evaluations of causal inference which included statistical significance and many other factors. These evaluations are already included in the PHG document (Section 6.2.1 and Table A7.23).

As also discussed in the PHG document, OEHHA evaluated the possible bias that might have been caused by the lack of information on past residences or drinking water consumption in the Vieira et al. (2013) exposure models. Please see Section 6.2.1 for a thorough discussion of this issue. Briefly, the fact that there was minimal improvement in the exposure model when individual drinking water consumption data were added provides good evidence that this information did not play an important role in the quality of these data. Also, the facts that the mean residential duration of the Vieira et al. (2013) cohort was fairly long (17 years) and that the Vieira et al. (2013) results were similar to those of Barry et al. (2013), which did include residential history, provides good evidence that the lack of residential history information in Vieira et al. (2013) was also not an important source of exposure data bias (Barry et al. 2013).

Comment 5: "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. 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.

"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."

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)

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

Response 5: Much of the information provided in the comment above is simply a description of the Barry et al. (2013) study, and relevant details of this study are already included in the PHG document (Sections 6.2.1 and Table A7.23).

The commenter mentions "additional follow up, refined exposure assessment, and larger cohort size" but provides no direct or compelling evidence that these improved the overall quality or validity of the Barry et al. (2013) study. With regards to "larger cohort size," statistical power is typically driven more by the number of cases included in the study than by overall cohort size (Beaumont and Breslow, 1981), and the Vieira et al. (2013) study had more than twice as many kidney cancer cases as Barry et al. (2013). Because of this, the larger cohort size in Barry et al. (2013) is not necessarily an advantage over the Vieira et al. (2013) study. With regards to "refined exposure assessment," please see the responses to the preceding comment regarding the drinking water consumption and residential history information included in the exposure model used by Barry et al. (2013). As noted, these particular data appeared to make

little difference in the accuracy or validity of the exposure model. Finally, with regards to the “additional follow-up” in Barry et al. (2013), the typical advantages of having a longer follow-up are the possibility that the number of cancer cases may be increased or the possibility that potentially longer cancer latency periods can be examined. However, neither of these issues prevented Vieira et al. (2013) from identifying clear associations between PFOA and cancer. As noted, Vieira et al. (2013) already included more than twice as many kidney cancer cases as Barry et al. (2013), and there was no indication that examining a longer cancer latency period was required to find clear associations. Overall, there is essentially no indication or reason to believe that Barry et al. (2013) was a markedly better study than Vieira et al. (2013).

The commenter states that the association between PFOA exposure and risk of kidney cancer is substantially reduced in Barry et al. (2013). However, this is not true in the analyses limited to community members (i.e., those who were not occupationally exposed to PFOA). This group made up almost 90% of the Barry et al. (2013) cohort. In this group, relative risk estimates of 1.95 and 2.04 were seen in the two highest exposure categories (when no lag period is used). This is very similar to Vieira et al. (2013) where the relative risk estimates in the two highest exposure categories were both 2.0. Although the exposure category boundaries were not provided for Barry et al. (2013), they were likely similar to those used in Vieira et al. (2013) since the two studies both took place in the US C8 study area. For PFOA workers, while the relative risk estimate in the highest exposure category was not elevated in Barry et al. (2013), the relative risk estimate in the second to the highest exposure category suggested about a 3- to 4-fold increase in risk. The reason why a clear association was not seen in the highest exposure category is unknown, but it could be related to the small sample size. While the number of cases in each category were not provided, there were only 18 cases of kidney cancer in the worker cohort as a whole in this study. This relatively small sample size means that the statistical power to identify true effects was likely much lower in workers than in the cohort of community members. This issue and other problems with the Barry et al. (2013) analyses of PFOA workers are discussed further in the response to the October 2021 public comments from the 3M Company (Comment 11).

Comment 6: “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.”

Response 6: Please see response to Comment 2 from this commenter.

Comment 7: “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). 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."

Response 7: Although clear monotonic responses were not observed in all the datasets, pancreatic islet cell carcinomas in male rats, hepatocellular adenomas in male and female rats, and the combined incidences of hepatocellular adenomas and carcinomas in female rats all had a statistically significant trend. Furthermore, pairwise comparisons indicated statistically significant differences in liver tumors in the high dose animals compared to controls. These data provide support that the tumors observed in the study are dose-related.

Comment 8: "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, suggests that the liver tumors observed by Butenhoff *et al.* 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. 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."

Response 8: The PHG draft document provides a very detailed MOA analysis for PFOS carcinogenesis in section 5.7.3. All available evidence for non-genotoxic and receptor activated mechanisms is considered, and an evaluation of the key characteristics of carcinogens for both PFOA and PFOS is presented. While the

commenter posits that "liver tumors in rats exposed to PFOS are ***likely*** caused by the activation of nuclear receptors such as PPARα, CAR, and PXR," (emphasis added) the evidence for this is also not sufficient for a stronger conclusion. OEHHA is not aware of any studies (e.g., cancer bioassays using PPARα, CAR, and PXR knockout animals) that demonstrate these receptor activation pathways as the only MOAs for PFOS carcinogenicity. Based on the available evidence, OEHHA concluded that PFOS should be evaluated as a carcinogen. This is supported by the decision of California's Carcinogen Identification Committee to list PFOS as a carcinogen under Proposition 65. Please also see response to Comment 3 from the California Association of Sanitation Agencies above.

Comment 9: "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."

Response 9: See responses to Comments 6 to 8 from this commenter. Tumor site concordance between species is not necessary for animal toxicity data to be considered relevant to humans.

Comment 10: "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.' 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."

Response 10: OEHHA agrees with the quotes from the US EPA provided by the commenter, although it should be noted that these were made in a very broad context and make no mention of serum cholesterol or hepatic enzyme levels (US EPA, 2022). Regardless, both serum cholesterol levels and hepatic enzyme concentrations have

clear linkages to apical or clinical outcomes. That is, higher levels of serum cholesterol are a well known and clear indicator of increased cardiovascular disease risk, and elevations in serum hepatic enzymes levels are a well known and clear clinical indicator of liver toxicity or damage. Sections 6.1.1 and 6.1.2 of the PHG document already include detailed discussions of these issues. Please also see response to Comment 44 from 3M company above.

Comment 11: "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. Based on its analysis, the Panel concluded that 'there was no evidence of a positive association between liver disease and estimated PFOA exposure.'"

Response 11: The commenter does not list any other "histological findings or functional tests for liver disease" that would be appropriate for use in a large scale human study and OEHHA is not aware of any. The other issues raised in this comment are already discussed in the PHG document (Section 6.1.1) and are also discussed in the responses to the October 2021 comments from the 3M Company (Comments 12 and 13). Briefly, increases in serum alanine aminotransferase (ALT) concentrations have been clearly linked to increases in both liver disease morbidity and mortality, and ALT concentrations are commonly used in the clinical evaluation and diagnosis of liver toxicity and liver disease (see Section 6.1.1 of the PHG document for references). These facts highlight the clinical importance of increases in serum levels of ALT and serve as the basis for OEHHA's decision to use this outcome in its noncancer PFOA dose-response calculations. While it is true that the C8 Science Panel did not identify an association between PFOA and liver disease in its study (Darrow et al. 2016), this study had some potential weaknesses. For example, a lack of sensitivity or specificity from using self-reported liver disease or from combining many different types of liver disease into one or two categories may have limited the ability of this study to identify a true effect. Further discussion of these weaknesses is provided in the response to the October 2021 comments from the 3M Company (Comment 13).

The C8 Science Panel report cited by the commenter did not include an evaluation of the potential or likely impacts that "small shifts" in liver function could have on a population basis, especially in a population like the US where nearly everyone has been exposed to PFOA (C8 Science Panel, 2012b; Calafat et al., 2007; Dong et al., 2019). In contrast, OEHHA has considered these broader effects and in the PHG document

(Section 5.2.5) has noted that "small effect sizes like this, which might have only minor or unnoticeable effects in an otherwise healthy individual, can have very important impacts on a population basis or in particularly susceptible people especially for very common exposures like PFOA."

Comment 12: "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. 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. 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. 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."

Response 12: OEHHA acknowledges that lipid homeostasis and fatty acid metabolism may be altered at a basal level in PPARα KO mice compared to WT. However, OEHHA did not state that PPARα-mediated liver effects in rodents have little relevance to humans. OEHHA does indicate that there is debate in the scientific community on this point, and that PFOA and PFOS act via multiple modes of action, of which PPARα activation is one.

Studies with PPARα KO mice provide important data on the specific downstream impacts (or lack thereof) of PPARα activation, particularly concerning effects in the liver. The commenter does not provide any specific examples where the results of studies reporting liver toxicity in PPARα KO mice should be questioned due to changes in lipid homeostasis or metabolism. As such, OEHHA has no reason to discount any results reported in PPARα KO mice. Furthermore, changes in gene expression between PPARα KO mice and WT are not entirely unexpected, as different physiological pathways are activated following PFOA exposure. It should be noted that Section 5.2.4 of the PHG document includes studies in which liver toxicity was observed in WT mice without PPARα activation (Rebholz et al., 2016; Li et al., 2017).

Comment 13: "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.'

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 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.' 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."

Response 13: Although the current literature on PFOS and cardiovascular disease (CVD) has been described as "mixed or primarily null" (US EPA, 2023d), a large, high quality study reporting convincing results, either positive or negative, has yet to be done. In contrast, increased cholesterol levels are a clear and well-known risk factor for CVD, and several high quality studies, including those used by OEHHA for its noncancer PFOS dose-response calculations, have reported clear and consistent associations between PFOS and increased cholesterol levels. Section 6.1.2 and Table A7.8 of the PHG document provide detailed information and discussions of this research.

As noted above, the Schillemans et al. (2022) study has now been added to the PHG document (Table A7.29) (Schillemans et al., 2022). This study evaluated prospective associations between serum PFOS concentrations and serum cholesterol levels among 631 adult study participants without prevalent myocardial infarction and stroke, and the positive associations identified support OEHHA's conclusion that PFOS increases serum cholesterol levels. The analyses of myocardial infarction (n= 345 cases) and stroke (n=354 cases) in this study involved smaller sample sizes and relatively low statistical power. In addition, as seen in Figures 3 and 4 of this publication, the findings for both stroke and myocardial infarction were mixed, making it difficult to draw strong conclusions about either of these outcomes. The authors also acknowledged several other potential weaknesses including potential confounding and the possibility that the use of cholesterol lowering medications could have masked some effects. Based on these and other weaknesses, the Schillemans et al. (2022) findings for myocardial infarction and stroke do not negate the use of serum cholesterol for PFOS dose-response assessment nor the strong evidence the Schillemans et al. (2022) study provided linking PFOS to higher serum cholesterol levels.

With regards to "the possibility that people with high cholesterol may retain PFOA," the only mention of this issue in the C8 Science Panel report is the following (C8 Science Panel, 2012a):

> "In C8 Science Panel work in the Mid-Ohio Valley, both analyses of exposure level by water district, and longitudinal follow-up of cholesterol analysed in relation to the

> degree of drop in PFOA serum levels, suggested that the association of PFOA and cholesterol is due to PFOA rather than confounding factors distorting the PFOA/cholesterol relationship or by cholesterol levels affecting PFOA level."

Thus, it appears that the C8 Science Panel mostly ruled out this possibility. Most importantly, the final conclusion of this Panel was that "there is a probable link between exposure to C8 (PFOA) and diagnosed high cholesterol (hypercholesterolemia)."

Comment 14: "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. 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."

Response 14: It is OEHHA's current policy to use a benchmark response (BMR) of 5% extra risk (unless there are data to suggest an alternate BMR should be used), as presented in OEHHA's peer-reviewed guidelines (OEHHA, 2008), and this has been done in several externally peer-reviewed PHGs. Also see Response 32 to the October 2021 comments from the American Chemistry Council and others.

Comment 15: "OEHHA also applied a body weight scaling factor to the human equivalent dose (HED) for PFOS, 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. (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."

Response 15: The body weight adjustment to the cancer slope factor is to account for interspecies differences. Without such adjustment, it would be implied that doses applied to animals would be equipotent in humans, which is incorrect. Since the use of animal serum concentrations (and not administered doses) would account for the toxicokinetic interspecies differences, the interspecies adjustment factor was reduced from $(BW_{animal}/BW_{human})^{1/4}$ to $(BW_{animal}/BW_{human})^{1/8}$ to adjust for remaining possible toxicodynamic differences.

Comment 16: "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. 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 evaluated the available information for the chemicals and concluded that an RSC of 50 to 60 percent is more appropriate.

"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. 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 and national serum concentration data from the National Health and Nutrition Examination Survey (NHANES). Correcting the RSC to appropriate data-driven values rather than the default makes a significant difference to the resulting PHG."

Response 16: Direct estimates of PFOA and PFOS produced an RSC of 20% or lower (see Table A5.2 in the PHG draft document). Different regulatory assessments may have different RSC estimates depending on a multitude of factors, including the levels in contaminated water, which can vary from area to area. Based on data from NHANES 2003/2004, Lorber and Egeghy (2011) estimated that dietary ingestion of PFOA was the primary route of exposure, with drinking water ingestion accounting for approximately 24% and 18% of the total exposure in adults and two-year-old children, respectively. These values are in line with the proposed RSC of 20%. Garnick et al. (2021) calculated an "actual" RSC of 93.5% using a reference dose of 20 ng/kg-day and a 95th percentile

ingestion dose of 1.31 ng/kg-day extrapolated from central tendency data from Lorber and Egeghy (2011). However, it is unclear how the RSC can be calculated from PFOA intake and a reference dose. Additionally, there were no validation data presented to indicate that the calculated 95th percentile intake actually reflects the corresponding serum values in the population. OEHHA's analysis of the RSC using the best available data indicated an RSC of 20% is optimal for PFOA and PFOS in California drinking water.

ELSINORE VALLEY MUNICIPAL WATER DISTRICT

Comment 1: "PHGs have significant impacts on public water system.

EVMWD encourages balancing the net impact of the real-world implications of the PHG while developing recommendations that can achieve positive public health outcomes, while continuing to provide safe drinking water at a reasonable cost to customers. There are impacts to water systems associated with any PHG published by OEHHA. The currently proposed limits for PFOA and PFOS are very low and while health data may support this level (studies are still not conclusive or long term), there would certainly be impacts to public water systems as they attempt to comply with an MCL that is set near this PHG. EVMWD asks that the State Water Resources Control Board (State Water Board) and OEHHA continue to consider the impacts on public water agencies should this PHG proceed as proposed.

Public water agencies will be required to report exceedances of substances for which no regulatory standard exists.

Public water systems are required to evaluate costs and consider implementing treatment to meet any PHG that is exceeded in their water system every three years. Such treatment is expensive, and it is essential that this PHG is developed towards enabling an MCL that protects public health, is effective, and feasible for public water agencies to comply with while keeping water affordable for customers. Water systems that are ineligible for or unsuccessful in obtaining financial support from the state have difficulty preventing increased burdens on already socioeconomically disadvantaged communities. Per the SWRCB, the average cost of water increased by 45% between 2007 and 2015. This has already forced low-income households to make difficult household decisions about water consumption to balance other expenses.

Public water agencies are tasked with the essential element of effective and factual communication with the public to maintain trust with their communities. PHGs are required to be reported in annual CCR's along with MCLs - sometimes creating confusion and concern. The currently proposed PHGs for PFOA and PFOS might raise concerns from consumers who are unsure what they mean for the safety of their water.

Public water agencies must also prioritize the Human Right to Water, which is often impacted by the increased cost threshold of complying with new MCLs."

Response 1: The cost of water treatment and feasibility for compliance are legitimate concerns that are addressed by the Water Board in the process of developing regulatory levels for chemical contaminants in drinking water.

A PHG is not a boundary line between safe and unsafe, but rather a goal that water systems should strive to achieve. Drinking water containing a chemical at levels exceeding its PHG can still be considered acceptable for public consumption. PHG technical support documents are publicly available, and OEHHA is available to answer questions from the public about PHGs. Potential confusion regarding the interpretation of PHG values is not a sufficient justification for changing peer reviewed PHG values that are based on sound science. Please also see response to Comment 1 from the California Association of Mutual Water Companies above.

Comment 2: "OEHHA should continue to follow the regulatory framework for developing PHGs and work with the State Water Board to follow the regulatory framework to develop MCLs.

Consistent with our previous comment letter, we encourage OEHHA to continue to make use of additional resources as they become available to inform the assessment of health risk effects of PFOA and PFOs in setting these PHG which will in turn increase the accuracy of the future recommended MCLs. OEHHA and the State Water Board Department of Drinking Water should continue to develop and provide clear communication about the meaning and purpose of PHGs which are complex and can be difficult for the public to understand.

As new information and epidemiological studies become available and potential health risks are better understood, OEHHA should maintain a regular review and update process for PHGs. For example, Table A5.1 in Appendix 5 suggest that food is a much more prominent source of PFOA exposure than water, but the PHG for PFOA acknowledges that there is not sufficient data to determine the impact that food packaging and nonstick cookware have on human exposure to PFAS. As information on this exposure route is developed, OEHHA should reexamine these PHGs."

Consistent with our prior comments on previous PHG rulemaking, EVMWD supports the development of PHGs based on the risk assessment of public health impacts from studies that are grounded in sound, credible science and research, are well-documented, and collect and analyze current data and information. EVMWD urges OEHHA to adhere to the best available, peer-reviewed practices, principles, and methods used by epidemiological professionals, including U.S. EPA's risk assessment team. As referenced in the past comment letters regarding development of this PHG, the PHG should be established using studies that reflect human consumption of PFAS-contaminated drinking water, exposure routes in tap drinking water, drinking water

consumption, and grouping PFAS compounds in groups based on shared and common health risk indicators."

Response 2: Per Health and Safety Code section 116365, PHGs are updated periodically. Thus, as more data on toxicity, exposure, or any other considerations become available, OEHHA will incorporate that information in subsequent PHG updates.

The PFOA and PFOS draft PHGs are based on sound science and were developed using the most current principles, practices, and methods for risk assessment. Furthermore, they underwent external scientific peer-review. The PHG for PFOA, and the noncancer health-protective concentrations for PFOA and PFOS, were derived from human studies, which directly reflect real-world exposures to PFOA and PFOS, including via drinking water. Consumption of contaminated drinking water and additional exposure routes from typical uses of tap water were considered when deriving these PHG values. Grouping PFAS chemicals that are similar in toxicokinetic and toxicological properties in humans is one option that OEHHA is exploring.

EASTERN MUNICIPAL WATER DISTRICT

Comment 1: "It is stated in the OEHHA Report that the proposed PHG will be a of maximum .007 parts per trillion ('PPT') for PFOA and maximum 1.00 PPT for PFOS. As a point of comparison, the U.S. EPA's proposed national primary drinking water regulation requires the concentration of either PFOA or PFOS must be below 4 parts per trillion. This PHG is a significantly more stringent standard that will lead to operational and financial burdens for water providers across the state.

Although the PHGs developed by OEHHA are not a legally enforceable standard, it is widely understood that the PHGs will inform a maximum contaminant level (MCL) to be created and enforced by the State Water Resources Control Board. In addition, to maintain trust among customers, if any source water exceeds a PHG, EMWD treats the water, or discontinues the use of the water source; serving water that exceeds the PHG is not a viable option. Costs that are incurred by water agencies having to meet these standards will undoubtedly be passed on the customers – including our economically disadvantaged, and severely disadvantaged communities, which comprise over one-third of our customers. For these reasons, EMWD would urge OEHHA to further consider adopting a PHG that aligns with the current federal standards."

Response 1: The commenter is correct that PHGs are not legally enforceable standards. A PHG is not a boundary line between safe and unsafe, but rather a goal that water systems should strive to achieve. Drinking water containing a chemical at levels exceeding its PHG can still be considered acceptable for public consumption. PHGs are solely based on human health considerations, and any issues related to MCLs and costs are best addressed by the Water Board. Please also see response to Comment 1 from the Association of California Water Agencies above.

Comment 2: "EMWD appreciates the opportunity to comment on this draft document and would like to reiterate that EMWD supports the goal of providing Californians access to safe, reliable, and affordable drinking water. However, these quality standards should seek to limit the harmful implications that will burden the customers and the communities that water utilities support."

Response 2: OEHHA acknowledges the comment. Any issues related to affordability and burden to customers should be brought to the Water Board. Please also see response to Comment 1 from the Association of California Water Agencies above.

ORANGE COUNTY WATER DISTRICT

Comment 1: "A comparison of Section 6.2.1 (Cancer Dose-Response-Analyses and Cancer Potency Derivation - PFOA) between the first and second drafts indicates minimal change where the additional information requested by OCWD would have been most appropriately included. We note some minor text additions justifying the selection of the Shearer et al. (2021) and Vieira et al. (2013) studies as the basis for the PHG over two other human epidemiological studies. However, most of our comments appear unaddressed, including those regarding: 1) OEHHA's direct use of published odds ratio (OR) quartiles unadjusted for other PFAS vs. a consideration of the studies' raw data to derive cancer slope factors (CSFs), 2) the basis for averaging the two CSFs when the studies used different serum determination methodologies (one-time measurement vs modeled), and 3) our request to include a corresponding serum value associated with human exposure to the PFOA PHG drinking water concentration, which would permit a comparison with the serum values described in the two supporting studies."

Response 1: Please see the responses to the October 2021 Comments 1 and 3 from the Orange County Water District. With regards to the decision to use published grouped findings rather than raw data, it should be noted that the use of published grouped data is common in environmental health risk assessment (US EPA 2023a). It should also be noted that the Shearer et al. (2021) and Vieira et al. (2013) findings underwent extensive internal and external peer review prior to publication. There were two major reasons why OEHHA did not request the raw data from the Shearer et al. (2021) and Vieira et al. (2013) studies. The first relates to confidentiality issues, and the possibility that breaches of participant privacy might occur as a result of the transfer, use, and long-term storage of research data. These breaches are possible even if standard protections are in place and even if personal information like names and addresses are removed (Patsakis and Lykousas 2023; Wolf et al. 2013). This does not mean that raw data should not be requested and used in some circumstances. However, it does mean that any advantages that might come from the use of raw data should be balanced against the possible adverse events that might result from data breaches and loss of research participant privacy. The second reason is that OEHHA judged that these raw data were not needed. This is because both studies were found to be of high quality (Table A7.29 and Section 6.2.1 of the PHG document) and both presented results that were highly detailed, comprehensive, and amenable to accurate dose-response analysis. A recent risk assessment by some of the C8 study and Shearer et al. (2021) authors supports this conclusion (Steenland et al. 2022). Steenland et al. (2022) combined the individual participant data from the Shearer et al. (2021) and Barry et al. (2013) studies to evaluate a number of different dose-response models for PFOA and renal cell carcinoma. Overall, the authors found that a linear dose-response model in the lower exposure range (i.e., the range of most general population exposures) provided a good fit to the underlying individual data. This supports OEHHA's finding that a linear model provided a good fit to the published grouped data (Section 6.2.1 and Figure 6.2.3), and therefore supports OEHHA's decision to use a linear model in its cancer slope factor (CSF) calculations. In addition, Steenland et al. (2022) reported a regression coefficient between serum PFOA and

renal cell carcinoma for the Shearer et al. (2021) study that was close to the one calculated using grouped data by OEHHA (0.089 vs. 0.098, respectively) (Table 6.2.7). That these two regression coefficients are similar is especially noteworthy given that different sets of adjustment factors were used. Steenland et al. (2022) only adjusted for hypertension and BMI, while Shearer et al. (2021) adjusted for hypertension, BMI, eGFR, previous freeze-thaw cycle, and calendar year of blood draw. Overall, given the high quality, comprehensive, and extensively peer-reviewed published grouped data that were available for both Shearer et al. (2021) and Vieira et al. (2013), OEHHA found little to no advantage to requesting and using the raw data from either of these two studies.

The basis for the decision to use the geometric mean of the CSFs derived from the Shearer et al. (2021) and Vieira et al. (2013) studies is that both were determined to be of very high quality, both provided the data needed for accurate risk assessment, and neither was considered to be more sensitive than the other. Based on these factors, OEHHA found no rationale for selecting one study over the other, and as such, both were included in the HPC calculations. While the methods used to assess exposure in these two studies differed, robust validation data showed that the modeled serum exposures used by Vieira et al. (2013) were well correlated with actual PFOA serum levels like those used in Shearer et al. (2021) (Shin et al. 2011). In addition, OEHHA's evaluations showed that possible errors from using these modeled exposure data were likely to be minor (Section 6.2.1 of the PHG document). Overall, there is no obvious reason why differences in the exposure metrics used in Shearer et al. (2021) and Vieira et al. (2013) would cause significant bias. A summary of these issues has now been added to Section 6.2.1 of the PHG document under the heading, *Summary of study selection*.

Regarding the PFOA serum concentration that corresponds to human exposure at the level of the PHG, OEHHA does not see the utility in providing that information. The PHG represents the PFOA concentration in drinking water where there is a one in one million extra risk of developing cancer. Serum concentrations at this level would be below the analytical level of detection, so there is no practical reason to include this information. Furthermore, deriving a serum concentration from the PHG value would not account for any additional exposures to PFOA in food, dust, or consumer products, and would not accurately reflect an exposed person's "true" serum concentration.

SAN JOAQUIN VALLEY DEMOCRATIC CLUB

Comment 1: "Since PFOA and PFOS can be filtered from drinking water and since it is present in many unavoidable ways on stain resistant surfaces, waterproofing and in cooking film, every effort should be made to require effective filtration in municipal water systems to reduce the growing and potentially deadly impact they have. Water systems that depend on wells in areas which may be prone to chemical use containing those chemical should not be sold without mandatory testing of water and indoor contamination in carpets, curtains and other interior materials. The accumulation of these and the PFAS chemicals together with other impacts have a major impact of public health levels of cancer. We cannot set the levels low enough."

Response 1: OEHHA acknowledges the comment.

NATURAL RESOURCES DEFENCE COUNCIL et al. [12]

General comment: "On July 14, 2023, OEHHA published in the California Regulatory Notice Register a notice announcing the availability of the second draft technical support document for the proposed Public Health Goals (PHGs) for PFOA and PFOS. The proposed PHGs for PFOA and PFOS remain unchanged from the first draft (published July 30, 2021): 0.007 parts per trillion (ppt) for PFOA based on kidney cancer in humans and 1 ppt for PFOS based on tumors in animal studies. These public health goals correspond to the OEHHA-calculated one-in-a-million risk values and represent the levels of these contaminants in drinking water that would 'pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.'

To date, the state of California has notification levels for PFOA, PFOS, PFHxS, and PFBS, but no maximum contaminant levels (MCLs) have been set for any PFAS or the class of PFAS combined. Although the development of public health goals for PFOA and PFOS is important, addressing all PFAS as a class is critically needed to protect Californians from contaminated drinking water.

Our organizations support OEHHA's scientific analysis and urge OEHHA to quickly finalize these PHGs so that the State Water Resources Control Board (SWRCB) can establish health-protective MCLs for PFOA and PFOS as soon as possible. Further, we urge OEHHA and the SWRCB to more efficiently protect public health by addressing all chemicals within the PFAS class.

- We support OEHHA's analysis of the most recent science and its use of the best available data and most current principles to arrive at the conclusion PFOA and PFOS can cause harm at extremely low levels (below current reporting limits), and
- We support the use of the best available science, including human epidemiological data, in both the PFOA and PFOS assessments, and
- We suggest to the SWRCB that PFAS be evaluated as a class and support establishing a class-based public health goal for PFAS."

Response: OEHHA acknowledges the comment. See response to Comment 3 below regarding the evaluation of PFAS as a class.

Comment 1: "We support the public health goal analysis and conclusion that PFOA and PFOS can cause harm at extremely low levels (below current reporting limits).

The scientific review and analysis, along with the resulting draft PHGs published by OEHHA, provides additional credence to the extreme toxicity of PFAS and is in alignment with current analyses by the United States Environmental Protection Agency

[12] Clean Water Action, Community Water Center, Breast Cancer Prevention Partners, Center For Public Environmental Oversight, Calpirg, Integrated Resource Management Inc, Erin Brokovich Foundation, National Stewardship Action Council, Women's Voices for The Earth, Leadership Council for Justice and Accountability, Green Science Policy Institute, Environmental Working Group, Center for Environmental Health, Responsible Purchasing Network, Heal the Bay, and Nh Science and Public Health

(US EPA). In March 2023, US EPA proposed maximum contaminant level goals (MCLGs) for PFOA and PFOS of 0 ppt based on the conclusion that both chemicals are 'likely carcinogenic.' US EPA's policy is to set MCLGs at zero for any non-threshold carcinogens. While OEHHA's approach to setting PHGs for carcinogens is slightly different, relying on cancer slope factors, the practical implications of both approaches and conclusions are that PFOA and PFOS can cause health harms, including cancer, and need to be strictly regulated to protect public health.

The proposed PHG analysis indicates that PFAS are potentially impacting numerous different health endpoints at low parts per trillion levels, including increased risk of kidney cancer, liver damage, increased cholesterol and immunotoxicity. Setting stringent PHGs is imperative for protecting against the increased risk of cancer, as well as the numerous other adverse health harms associated with PFOA and PFOS. Although PHGs are non-enforceable, they are a critical step in the development of MCLs, by establishing the goal level which should be aspired to in order to protect public health."

Response 1: OEHHA acknowledges the comment.

Comment 2: "We support the use of the best available science, including human epidemiological data, in both the PFOA and PFOS assessments.

An expansive body of scientific literature reaching back more than three decades links increased PFOA exposure to increased rates of cancer. These findings are drawn from studies in animals and workers, and of exposed communities. In 2012, the C8 Science Panel study of nearly 70,000 exposed community members living near the Parkersburg, W.V., DuPont facility found a probable link between PFOA exposure and testicular and kidney cancer.

We strongly support the use of human epidemiological data that links PFOA to kidney cancer as the basis for the PHG. These assessments are in accordance with the EPA's Guidelines for Carcinogenic Risk Assessment:

> Epidemiologic data are extremely valuable in risk assessment because they provide direct evidence on whether a substance is likely to produce cancer in humans…When human data of high quality and adequate statistical power are available, they are generally preferable over animal data and should be given greater weight in hazard characterization and dose-response assessment, although both can be used.

Both human epidemiological studies used in OEHHA's dose response analysis had large numbers of participants with representative exposure levels of the general population. The study by Shearer et al. included renal cell carcinoma cases identified from a randomized screening trial of 150,000 adults, and Viera et al. identified cases from 13 counties in Ohio and West Virginia from an estimated population study area of 500,000. PFOA exposure was assessed directly using measured serum levels of

individuals (Shearer et al.), a good indicator of long-term exposure, and Viera et al. estimated PFOA levels using a validated exposure model. Both studies showed evidence of a dose-response relationship. The findings of these studies are also consistent with two other human studies that show a strong association between PFOA and kidney cancer.

We agree that studies in animals also support the carcinogenicity of PFOA to humans. The National Toxicology Program's 2020 report 'NTP Technical Report on the Toxicology and Carcinogenesis Studies of Perfluorooctanoic Acid (CASRN 335-67-1) Administered in Feed to Sprague Dawley Rats' concluded, following two-year feeding studies, that PFOA causes cancer in male rats. The NTP study found 'clear evidence of carcinogenic activity' and that PFOA exposure increased the incidence of tumors in liver and pancreas in male rats. The NTP findings supported the proposed listing of PFOA as a carcinogen in the first draft PHG document and under California Proposition 65 (Prop65).

Epidemiological studies were informative in evaluating the non-cancer risk of PFOS, including in particular the increased cholesterol levels observed in the C8 study. In the absence of a large sample-size epidemiological study evaluating cancer endpoints, OEHHA used the Key Characteristics of Carcinogens Framework to evaluate and conclude that PFOS is carcinogenic. We continue to support his approach and note that it is in agreement with the findings of the Carcinogen Identification Committee's State Qualified Experts, which listed PFOS as a carcinogen under Prop65 in December 2021."

Response 2: OEHHA acknowledges the comment, and agrees that the epidemiology and animal toxicity data support evaluating PFOA and PFOS as carcinogens.

Comment 3: "PFAS should be evaluated as a class, and California should consider establishing a class based public health goal.

Although we understand that OEHHA developed the proposed PHGs for PFOA and PFOS at the request of the SWRCB, this only represents a small step toward protecting public health. Consequently, our organizations urge the SWRCB and OEHHA to prioritize review of PFAS beyond the long chain PFAS compounds to include the entire class of chemicals. California's Environmental Contaminant Biomonitoring Program lists the entire class of PFAS as priority chemicals for measuring it in the blood and urine of Californians, and has proposed to expand this class to include all carbon-fluorine bond containing substances. This is in part due to the persistence conferred to chemicals containing carbon-fluorine bonds and that it is a resource efficient approach, facilitating the use of non-targeted laboratory screening methods for chemicals with carbon-fluorine bonds. The Department of Toxic Substances Control also applies the class approach to prioritizing chemicals within the Safer Consumer Products program and supports extending this approach to other regulatory agencies to focus on this entire class of chemicals with similar hazard traits. This framework is necessary to avoid regrettable substitutions and manage a persistent, structurally similar class that includes thousands

of chemicals. Further, other PFAS that have been studied, beyond PFOA and PFOS, such as the replacement chemical GenX, have shown evidence of carcinogenicity in two-year animal studies."

US EPA has taken the first steps towards a class-based approach for addressing PFAS in drinking water. In March 2023 US EPA proposed MCLs for PFOA and PFOS as well as a Hazard Index for 4 additional PFAS (PFBS, GenX, PFNA, and PFHxS). While we are pleased with the acknowledgment that exposure to multiple PFAS can have an additive effect, we urge OEHHA and the SCRWB to address PFAS in drinking water more comprehensively. Such actions are necessary because of the large fraction of unknown PFAS in drinking water sources, which will continue to be an issue as long as PFAS are in production and use.

Our organizations are deeply concerned about the prevalence of all types of PFAS detected in drinking water and the continued wide scale contamination in the environment. Analyzing state and federal data, it is estimated that more than 200 million Americans, including up to 22 million Californians, could have PFAS-contaminated drinking water. Analysis has also identified more than 57,000 presumptive contamination sites across the nation. In addition to the environmental exposures to PFOA and PFOS that continue to affect the health and safety of California's residents despite their phase-out, there is growing evidence that the replacement chemicals that continue to be approved for use are just as harmful to human health and the environment. Multiple toxicity assessments of other PFAS have been performed by EPA, all documenting a range of health effects associated with PFAS exposure. For instance, GenX and PFBS have been linked to health effects similar to those caused by the chemicals they have replaced (PFOA and PFOS, respectively).

Due to income and health disparities, low-income communities and communities of color are especially vulnerable to PFOA, PFOS and broader PFAS exposure, although few studies have been conducted to characterize disparities. A report analyzing California's PFAS drinking water monitoring data revealed that PFAS pollution in California is widespread throughout the state, but more intense in communities already overburdened by multiple sources of pollution and by other factors that make them more sensitive to pollution, putting those vulnerable communities at greater risk of harm from PFAS exposure. At least 69 percent of state-identified disadvantaged communities have PFAS contamination in their public water systems. Almost a quarter of these communities face the highest levels of PFAS contamination in the state. A more recent study using monitoring data from 18 states found that communities of color are more likely to be exposed to harmful levels of PFAS in their water supplies than people living in other communities.

Finally, by focusing only on two chemicals, both of which are long-chain PFAS, water systems are likely to invest in treatment that will not be optimized to treat short-chain PFAS that are similarly toxic. As a result, systems may have to spend additional money to address these other PFAS chemicals, placing a tremendous economic burden on ratepayers and potentially limiting actions that could be taken against PFAS

manufacturers to recoup treatment costs. California's limited approach is, therefore, shortsighted and fails to consider the overall health and fiscal impacts of PFAS on communities."

Response 3: OEHHA acknowledges the concern of regulating PFAS as a class. Grouping PFAS with similar toxicological and kinetics profiles is something that OEHHA is currently evaluating.

Comment 4: "In conclusion, our organizations support the development of PHGs for PFOA and PFOS at 0.007 ppt and 1 ppt, respectively, and strongly encourage OEHHA to finalize these PHGs quickly so that efforts can be focused on addressing the risk of health harms for the entire class of PFAS."

Response 4: OEHHA acknowledges the comment.

MONARCH ACTION

General comment: "In the Second Public Review Draft, published July 2023, OEHHA states the purpose of PHGs are to 'estimate the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming water on a daily basis over a lifetime'. MONARCH supports OEHHA's proposed PHGs for PFOA (0.007 parts per trillion) and PFOS (1 ppt) which are rooted in the most recent and relevant studies.

MONARCH also supports OEHHA's proposed health protective drinking water concentrations for noncancer health effects for both PFOA (3 ppt, based on increased risk of liver damage in humans) and PFOS (2 ppt based on increased total cholesterol in humans). **However, MONARCH strongly encourages OEHHA to extend the PHG levels to all chemicals in this PFAS toxic class, not just PFOA/PFOS.**"

Response: OEHHA acknowledges the comment. See response to Comment 4 below regarding the evaluation of PFAS as a class.

Comment 1: "*Levels of toxic PFOA/PFOS (as well as other chemicals belonging to this class) should be as low as detectibly possible to minimize lifetime exposure and developmental impacts to children*.

The public draft document showcases the ways in which PFOA and PFOS are known to bioaccumulate in human tissues. As it is well known, children are a toxicologically more sensitive endpoint than adults. They are smaller and live longer from any given time of exposure than the general adult population. This makes PFOA/PFOS exposure even more pernicious: First, it is more likely to cause harm when you compare the relative sizes of the affected organs to adult populations; and second, longitudinally speaking, more of the toxins will accumulate in their bodies over their lifetimes. Exposure to PFOS is linked to behavioral alterations, learning/memory impairment, and changes in chemical signaling, while PFOA exposure has been linked to ADHD. Therefore, MONARCH strongly advocates for stringent PHG levels of toxic PFAS chemicals to prevent further exposure for children."

Response 1: OEHHA acknowledges the comment.

Comment 2: "*PFOA and PFOS can cross the placenta and accumulate in the fetus, and can also transfer via breast milk. These chemicals are known liver and neurotoxins, and can therefore impact a child's overall development*.

Setting strict PHGs relating to these toxic chemicals will reduce exposure for both lactating mothers and children. Fetal livers are a child's major hematopoietic organ during development; therefore, it is vital to prevent known liver toxins from bioaccumulating in developing tissues. The data provided in the second draft document states that 'the half-life of PFOA is 2.3 years, whereas PFOS is 5.4 years…' and that 'organisms with greater half-lives would bioaccumulate the compound to a greater

extent'. Since a fetus is an even more toxicologically sensitive endpoint than the children discussed above, preventing exposure to toxins in utero is of utmost importance.

Children receive their earliest immunity from breast milk. OEHHA studies highlighted in previous public workshops showcase the dangers to immune system functioning when impeded by PFOA/PFOS – '[s]uppression in one or more measure of anti-vaccine antibody response associated with prenatal, childhood, and adult exposures; 'PFOA increased asthma, total IgE, rhinitis'; 'ulcerative colitis an autoimmune disease in the colon/rectum'; '[d]ecreased levels of immune cells; increased histamine and TNF-α'. MONARCH stands behind OEHHA's commitment to protect vulnerable communities when setting their goals."

Response 2: OEHHA acknowledges the comment.

Comment 3: "*Preeclampsia is one of the leading causes of maternal death worldwide; it affects 1 in 25 pregnancies in the US. Black women are 60% more likely to suffer from preeclampsia and communities of color are more likely to be exposed to PFAS chemicals in their water*.

Finally, MONARCH must comment on OEHHA's statement re: 'evidence of an association with risk of preeclampsia and pregnancy-related hypertension' regarding PFOA/PFOS. OEHHA identified six studies published since 2016 discussing the association between PFOA/PFOS exposure and preeclampsia (one of which also discusses PFNA). As an organization, we urge OEHHA to consider all PFAS class chemicals when establishing these public health goals.

PFOA/PFOS are known to cause 'adverse developmental effects includ[ing] reduced pup body weight, developmental delays, and altered hormone and glucose regulation in rats.' As noted above, these chemicals bioaccumulate in humans. The CDC notes that as many as '1 in 20 pregnant women has gestational diabetes. It is more common in Native American, Alaskan Native, Hispanic, Asian, and Black women', suggesting that hormone and glucose regulation in communities of color would further be impacted without strict regulations of PFOA and PFOS. Income and health disparities already disproportionately affect low-income communities, communities of color, and disabled individuals. Exposure to PFOA, PFOS, and broader PFAS, are no exception, and therefore, OEHHA should take extra care to protect vulnerable individuals."

Response 3: OEHHA acknowledges the comment. Pursuant to Health and Safety Code 116365, OEHHA is mandated to consider susceptible populations, including infants and children, when developing PHGs.

Comment 4: "The available science supports OEHHA's PHG of 0.007 ppt for PFOA and 1 ppt for PFOS, as well as the non-cancer PHGs. We believe, by establishing these PHGs, OEHHA is taking a critical step toward protecting all Californians. Moreover, we

urge OEHHA to consider setting public health goals for PFAS as a class, as this would be a more protective public health measure."

Response 4: OEHHA acknowledges the concern regarding PFAS as a class. OEHHA is currently evaluating the possibility of grouping PFAS with similar toxicological and kinetic profiles.

REFERENCES CITED IN RESPONSES

Aarts MJ, van der Aa MA, Coebergh JW, Louwman WJ (2010). Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 46(14): 2633-2646.

Abbas AK, Lichtman AH, Pillai S. 2014. *Cellular and molecular immunology E-book*, Elsevier Health Sciences.

Abraham K, Mielke H, Fromme H, et al. (2020). Internal exposure to perfluoroalkyl substances (PFASs) and biological markers in 101 healthy 1-year-old children: associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. *Arch Toxicol* 94(6): 2131-2147.

Ahluwalia IB, Morrow B, Hsia J (2005). Why do women stop breastfeeding? Findings from the Pregnancy Risk Assessment and Monitoring System. *Pediatrics* 116(6): 1408-1412.

Alderete TL, Jin R, Walker DI, et al. (2019). Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: A proof-of-concept analysis. *Environ Int* 126: 445-453.

Alexander B, Olsen G, Burris J, Mandel J, Mandel J (2003). Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occupational and environmental medicine* 60(10): 722-729.

Alexander BH, Olsen GW (2007). Bladder cancer in perfluorooctanesulfonyl fluoride manufacturing workers. *Annals of Epidemiology* 17(6): 471-478.

Altman DG, Bland JM (1995). Statistic notes: the normal distribution. *BMJ* 310(6975): 298.

Altman DG, Bland JM (2003). Interaction revisited: the difference between two estimates. BMJ 326(7382):219.

American Cancer Society (2018). "What Causes Testicular Cancer?" https://www.cancer.org/cancer/testicular-cancer/causes-risks-prevention/what-causes.html [accessed April 6, 2022.

American Public Health Association (2016). Reducing Human Exposure to Highly Fluorinated Chemicals to Protect Public Health.

Andersen ME, Hagenbuch B, Apte U, et al. (2021b). Why is elevation of serum cholesterol associated with exposure to perfluoroalkyl substances (PFAS) in humans? A workshop report on potential mechanisms. *Toxicology* 459: 152845.

Andersen ME, Mallick P, Clewell HJ, 3rd, et al. (2021). Using quantitative modeling tools to assess pharmacokinetic bias in epidemiological studies showing associations between biomarkers and health outcomes at low exposures. *Environ Res* 197: 111183.

Andrews DQ, Naidenko OV (2020). Population-wide exposure to per-and polyfluoroalkyl substances from drinking water in the United States. *Environmental science & technology letters* 7(12): 931-936.

Angrisani L, Santonicola A, Iovino P, et al. (2017). Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. *Obes Surg* 27(9): 2279-2289.

ATSDR (2018). Toxicological Profile for Perfluoroalkyls. Draft for Public Comment. Agency for Toxic Substances and Disease Registry.

ATSDR (2021). Toxicological Profile for Perfluoroalkyls. Agency for Toxic Substances and Disease Registry.

Averina M, Brox J, Huber S, Furberg AS (2021). Exposure to perfluoroalkyl substances (PFAS) and dyslipidemia, hypertension and obesity in adolescents. The Fit Futures study. *Environ Res* 195: 110740.

Axelson O (1978). Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health* 4(1): 98-102.

Bălan SA, Mathrani VC, Guo DF, Algazi AM (2021). Regulating PFAS as a chemical class under the California Safer Consumer Products Program. *Environmental health perspectives* 129(2): 025001.

Ballesteros V, Costa O, Iniguez C, et al. (2017). Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. *Environ Int* 99: 15-28.

Banjabi AA, Li AJ, Kumosani TA, Yousef JM, Kannan K (2020). Serum concentrations of perfluoroalkyl substances and their association with osteoporosis in a population in Jeddah, Saudi Arabia. *Environ Res* 187: 109676.

Bao J, Zhang Y, Zhang L, Wang X (2021). Effects of maternal exposure to PFOA on testes of male offspring mice. *Chemosphere* 272: 129585.

Barry V, Winquist A, Steenland K (2013). Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environmental health perspectives* 121(11-12): 1313-1318.

Bartell SM, Calafat AM, Lyu C, et al. (2010). Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. *Environmental health perspectives* 118(2): 222-228.

Bartell SM, Vieira VM (2021). Critical review on PFOA, kidney cancer, and testicular cancer. *Journal of the Air & Waste Management Association* 71(6): 663-679.

Beaumont JJ, Breslow NE (1981). Power considerations in epidemiologic studies of vinyl chloride workers. Am J Epidemiol 114(5): 725-734.

Becker RA, Dellarco V, Seed J, et al. (2017b). Quantitative weight of evidence to assess confidence in potential modes of action. *Regulatory Toxicology and Pharmacology* 86: 205-220.

Becker RA, Dreier DA, Manibusan MK, et al. (2017a). How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? *Regulatory Toxicology and Pharmacology* 90: 185-196.

Beesoon S, Genuis SJ, Benskin JP, Martin JW (2012). Exceptionally high serum concentrations of perfluorohexanesulfonate in a Canadian family are linked to home carpet treatment applications. *Environmental science & technology* 46(23): 12960-12967.

Behr A-C, Plinsch C, Braeuning A, Buhrke T (2020). Activation of human nuclear receptors by perfluoroalkylated substances (PFAS). *Toxicology in Vitro* 62: 104700.

Bernstein AS, Kapraun DF, Schlosser PM (2021). A model template approach for rapid evaluation and application of physiologically based pharmacokinetic models for use in human health risk assessments: a case study on per-and polyfluoroalkyl substances. *Toxicological Sciences* 182(2): 215-228.

Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC (2001). Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicological Sciences* 60(1): 44-55.

Birnbaum LS (2019). Testimony for hearing on "Examining the Federal Response to the risks associated with per- and polyfluoroalkyl substances (PFAS)." Testimony before the Senate Committee on Environmental and Public Works, March 28, 2019. Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences: Washington, DC.

Birnbaum LS, Grandjean P (2015). Alternatives to PFASs: perspectives on the science, NLM-Export. 123**:** A104-A105.

Birukov A, Andersen LB, Andersen MS, et al. (2021). Exposure to perfluoroalkyl substances and blood pressure in pregnancy among 1436 women from the Odense Child Cohort. *Environment International* 151: 106442.

Bjork J, Butenhoff J, Wallace KB (2011). Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. *Toxicology* 288(1-3): 8-17.

Bjork JA, Wallace KB (2009). Structure-activity relationships and human relevance for perfluoroalkyl acid–induced transcriptional activation of peroxisome proliferation in liver cell cultures. *Toxicological Sciences* 111(1): 89-99.

Blake KD, Moss JL, Gaysynsky A, Srinivasan S, Croyle RT (2017). Making the Case for Investment in Rural Cancer Control: An Analysis of Rural Cancer Incidence, Mortality, and Funding Trends. *Cancer Epidemiol Biomarkers Prev* 26(7): 992-997.

Blum A, Balan SA, Scheringer M, et al. (2015). The Madrid statement on poly-and perfluoroalkyl substances (PFASs). *Environmental health perspectives* 123(5): A107-A111.

Bonefeld-Jorgensen EC, Long M, Fredslund SO, Bossi R, Olsen J (2014). Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. *Cancer Causes Control* 25(11): 1439-1448.

Borghese MM, Walker M, Helewa ME, Fraser WD, Arbuckle TE (2020). Association of perfluoroalkyl substances with gestational hypertension and preeclampsia in the MIREC study. *Environment International* 141: 105789.

Brockwell SE, Gordon IR (2001). A comparison of statistical methods for meta-analysis. *Stat Med* 20(6): 825-840.

Bruell JH, Daroczy AF, Hellerstein HK (1962). Strain and sex differences in serum cholesterol levels of mice. *Science* 135(3508): 1071-1072.

Buck Louis GM, Zhai S, Smarr MM, et al. (2018). Endocrine disruptors and neonatal anthropometry, NICHD Fetal Growth Studies - Singletons. *Environ Int* 119: 515-526.

Buckley JP, Kuiper JR, Lanphear BP, et al. (2021). Associations of maternal serum perfluoroalkyl substances concentrations with early adolescent bone mineral content and density: the Health Outcomes and Measures of the Environment (HOME) study. *Environmental health perspectives* 129(9): 097011.

Budtz-Jorgensen E and Grandjean P (2018). Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity. *PLoS One* 13(10): e0205388.

Buhrke T, Kibellus A, Lampen A (2013). In vitro toxicological characterization of perfluorinated carboxylic acids with different carbon chain lengths. *Toxicology letters* 218(2): 97-104.

Buhrke T, Krüger E, Pevny S, et al. (2015). Perfluorooctanoic acid (PFOA) affects distinct molecular signalling pathways in human primary hepatocytes. *Toxicology* 333: 53-62.

Bulka CM, Avula V, Fry RC (2021). Associations of exposure to perfluoroalkyl substances individually and in mixtures with persistent infections: Recent findings from NHANES 1999-2016. *Environ Pollut* 275: 116619.

Bus JS (2017). IARC use of oxidative stress as key mode of action characteristic for facilitating cancer classification: Glyphosate case example illustrating a lack of robustness in interpretative implementation. *Regulatory Toxicology and Pharmacology* 86: 157-166.

Butenhoff J, Costa G, Elcombe C, et al. (2002). Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicological Sciences* 69(1): 244-257.

Butenhoff JL, Chang S-C, Olsen GW, Thomford PJ (2012a). Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. *Toxicology* 293(1-3): 1-15.

Butenhoff JL, Kennedy GL, Chang S-C, Olsen GW (2012b). Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague–Dawley rats. *Toxicology* 298(1): 1-13.

Butenhoff JL, Pieterman E, Ehresman DJ, et al. (2012c). Distribution of perfluorooctanesulfonate and perfluorooctanoate into human plasma lipoprotein fractions. *Toxicol Lett* 210(3): 360-365.

C8 Science Panel (2012). Probable Link Evaluation for Heart Disease (Including High Blood Pressure, High Cholesterol, Coronary Artery Disease). Report Number.:Government Body http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Heart_Disease_29Oct2012.pdf.

Calafat AM, Kuklenyik Z, Reidy JA, et al. (2007). Serum concentrations of 11 polyfluoroalkyl compounds in the u.s. population: data from the national health and nutrition examination survey (NHANES). *Environ Sci Technol* 41(7): 2237-2242.

Canova C, Barbieri G, Jeddi MZ, et al. (2020). Associations between perfluoroalkyl substances and lipid profile in a highly exposed young adult population in the Veneto Region. *Environment International* 145: 106117.

Canova C, Barbieri G, Zare Jeddi M, et al. (2020). Associations between perfluoroalkyl substances and lipid profile in a highly exposed young adult population in the Veneto Region. *Environ Int* 145: 106117.

Cao T, Qu A, Li Z, et al. (2021). The relationship between maternal perfluoroalkylated substances exposure and low birth weight of offspring: a systematic review and meta-analysis. *Environmental Science and Pollution Research* 28(47): 67053-67065.

Cattley RC, Cullen JM. 2013. *Liver and gall bladder*. Toxicologic pathology. CGRaMAW W.M. Haschek. New York, Elsevier**:** 1509-1566.

Caverly Rae J, Craig L, Slone TW, et al. (2015). Evaluation of chronic toxicity and carcinogenicity of ammonium 2, 3, 3, 3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in Sprague–Dawley rats. *Toxicology reports* 2: 939-949.

Ceriotti F, Henny J, Queraltó J, et al. (2010). Common reference intervals for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) in serum: results from an IFCC multicenter study. *Clinical chemistry and laboratory medicine* 48(11): 1593-1601.

Chang S, Allen BC, Andres KL, et al. (2017). Evaluation of serum lipid, thyroid, and hepatic clinical chemistries in association with serum perfluorooctanesulfonate (PFOS) in cynomolgus monkeys after oral dosing with potassium PFOS. *Toxicological Sciences* 156(2): 387-401.

Charles D, Berg V, Nost TH, et al. (2020). Pre- and post-diagnostic blood profiles of perfluoroalkyl acids in type 2 diabetes mellitus cases and controls. *Environ Int* 145: 106095.

Château-Degat M-L, Pereg D, Dallaire R, et al. (2010). Effects of perfluorooctanesulfonate exposure on plasma lipid levels in the Inuit population of Nunavik (Northern Quebec). *Environmental research* 110(7): 710-717.

Chen A, Jandarov R, Zhou L, et al. (2019). Association of perfluoroalkyl substances exposure with cardiometabolic traits in an island population of the eastern Adriatic coast of Croatia. *Sci Total Environ* 683: 29-36.

Chen S-H, Chao P-M (2017). Prenatal PPARα activation by clofibrate increases subcutaneous fat browning in male C57BL/6J mice fed a high-fat diet during adulthood. *PloS one* 12(11): e0187507.

Chen S-L, Jones LK, Jackson M (2018). Childbearing and quality of life decisions for women in Taiwan. *Int. J. Healthcare* 4: 16-24.

Chen Z, Yang T, Walker DI, et al. (2020). Dysregulated lipid and fatty acid metabolism link perfluoroalkyl substances exposure and impaired glucose metabolism in young adults. *Environ Int* 145: 106091.

Cheung C, Akiyama TE, Ward JM, et al. (2004). Diminished hepatocellular proliferation in mice humanized for the nuclear receptor peroxisome proliferator-activated receptor α. *Cancer research* 64(11): 3849-3854.

Chiu WA, Guyton KZ, Martin MT, Reif DM, Rusyn I (2018). Use of high-throughput in vitro toxicity screening data in cancer hazard evaluations by IARC Monograph Working Groups. *Altex* 35(1): 51.

Christensen KY, Raymond M, Meiman J (2019). Perfluoroalkyl substances and metabolic syndrome. *Int J Hyg Environ Health* 222(1): 147-153.

Cluett R, Seshasayee SM, Rokoff LB, et al. (2019). Per- and Polyfluoroalkyl Substance Plasma Concentrations and Bone Mineral Density in Midchildhood: A Cross-Sectional Study (Project Viva, United States). *Environ Health Perspect* 127(8): 87006.

Colli JL, Busby JE, Amling CL (2009). Renal cell carcinoma rates compared with health status and behavior in the United States. *Urology* 73(2): 431-436.

Consonni D, Straif K, Symons JM, et al. (2013). Cancer risk among tetrafluoroethylene synthesis and polymerization workers. *Am J Epidemiol* 178(3): 350-358.

Convertino M, Church TR, Olsen GW, et al. (2018). Stochastic pharmacokinetic-pharmacodynamic modeling for assessing the systemic health risk of perfluorooctanoate (PFOA). *Toxicol Sci* 163(1): 293-306.

Córdoba J, O'Riordan K, Dupuis J, Borensztajn J, Blei AT (1998). Diurnal variation of serum alanine transaminase activity in chronic liver disease. *Hepatology* 28(6): 1724-1725.

Corton JC, Cunningham ML, Hummer BT, et al. (2014). Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPAR α) as a case study. *Critical reviews in toxicology* 44(1): 1-49.

Costa G, Sartori S, Consonni D (2009). Thirty years of medical surveillance in perfluorooctanoic acid production workers. *Journal of occupational and environmental medicine*: 364-372.

Costello E, Rock S, Stratakis N, et al. (2022). Exposure to per- and Polyfluoroalkyl Substances and Markers of Liver Injury: A Systematic Review and Meta-Analysis. *Environ Health Perspect* 130(4): 46001.

Coughlin SS, Neaton JD, Randall B, Sengupta A (1997). Predictors of mortality from kidney cancer in 332,547 men screened for the Multiple Risk Factor Intervention Trial. *Cancer* 79(11): 2171-2177.

Council of the European Union (2019). Towards a Sustainable Chemicals Policy Strategy of the Union. Brussels, Belgium.

Cousins IT, DeWitt JC, Glüge J, et al. (2020). Strategies for grouping per-and polyfluoroalkyl substances (PFAS) to protect human and environmental health. *Environmental Science: Processes & Impacts* 22(7): 1444-1460.

Dalsager L, Christensen N, Halekoh U, et al. (2021). Exposure to perfluoroalkyl substances during fetal life and hospitalization for infectious disease in childhood: A study among 1,503 children from the Odense Child Cohort. *Environment International* 149: 106395.

Darrow LA, Groth AC, Winquist A, et al. (2016). Modeled perfluorooctanoic acid (PFOA) exposure and liver function in a mid-Ohio valley community. *Environ Health Perspect* 124(8): 1227-1233.

Deb S, Puthanveetil P, Sakharkar P (2018). A population-based cross-sectional study of the association between liver enzymes and lipid levels. *International Journal of Hepatology* 2018.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials* 7(3): 177-188.

Dewitt J, Cox K, Savitz D (2019). Health-based drinking water recommendation for drinking water value recommendations in Michigan.

Di Nisio A, De Rocco Ponce M, Giadone A, et al. (2020). Perfluoroalkyl substances and bone health in young men: a pilot study. *Endocrine* 67(3): 678-684.

Di Nisio A, Rocca M, Sabovic I, et al. (2020). Perfluorooctanoic acid alters progesterone activity in human endometrial cells and induces reproductive alterations in young women. *Chemosphere* 242: 125208.

Dietschy JM, Turley SD, Spady DK (1993). Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. *Journal of lipid research* 34(10): 1637-1659.

Dillberger JE (1994). Age-related pancreatic islet changes in Sprague-Dawley rats. *Toxicologic pathology* 22(1): 48-55.

Doe JE, Boobis AR, Dellarco V, et al. (2019). Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. *Regulatory Toxicology and Pharmacology* 103: 124-129.

Donat-Vargas C, Bergdahl IA, Tornevi A, et al. (2019). Associations between repeated measure of plasma perfluoroalkyl substances and cardiometabolic risk factors. *Environ Int* 124: 58-65.

Dong G-H, Zhang Y-H, Zheng L, et al. (2009). Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. *Archives of toxicology* 83(9): 805-815.

Dong Z, Wang H, Yu YY, et al. (2019). Using 2003-2014 U.S. NHANES data to determine the associations between per- and polyfluoroalkyl substances and cholesterol: Trend and implications. *Ecotoxicol Environ Saf* 173: 461-468.

Dourson ML, Gadagbui B, Onyema C, McGinnis PM, York RG (2019). Data derived extrapolation factors for developmental toxicity: A preliminary research case study with perfluorooctanoate (PFOA). *Regulatory Toxicology and Pharmacology* 108: 104446.

Duan Y, Sun H, Yao Y, Meng Y, Li Y (2020). Distribution of novel and legacy per-/polyfluoroalkyl substances in serum and its associations with two glycemic biomarkers among Chinese adult men and women with normal blood glucose levels. *Environ Int* 134: 105295.

Dzierlenga MW, Keast DR, Longnecker MP (2021). The concentration of several perfluoroalkyl acids in serum appears to be reduced by dietary fiber. *Environment International* 146: 106292.

EFSA (2018). Risk to Human Health Related to the Presence of Perfluorooctane Sulfonic Acid and Perfluorooctanoic Acid in Food. *EFSA Journal* 16(12).

EFSA (2020). Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA Journal* 18(9): e06223. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6223 [accessed 11/02/21.

Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315(7109): 629-634.

Elcombe CR, Elcombe BM, Foster JR, et al. (2012a). 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. *Toxicology* 293(1-3): 16-29.

Elcombe CR, Elcombe BM, Foster JR, et al. (2012b). Evaluation of hepatic and thyroid responses in male Sprague Dawley rats for up to eighty-four days following seven days of dietary exposure to potassium perfluorooctanesulfonate. *Toxicology* 293(1-3): 30-40.

Elcombe CR, Elcombe BM, Foster JR, et al. (2010). Hepatocellular hypertrophy and cell proliferation in Sprague–Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPARα and CAR/PXR. *Archives of toxicology* 84(10): 787-798.

Elcombe CR, Peffer RC, Wolf DC, et al. (2014). Mode of action and human relevance analysis for nuclear receptor-mediated liver toxicity: A case study with phenobarbital as a model constitutive androstane receptor (CAR) activator. *Critical reviews in toxicology* 44(1): 64-82.

Emmett EA, Zhang H, Shofer FS, et al. (2006). Community exposure to perfluorooctanoate: relationships between serum levels and certain health parameters. *Journal of occupational and environmental medicine/American College of Occupational and Environmental Medicine* 48(8): 771.

Eriksen KT, Raaschou-Nielsen O, McLaughlin JK, et al. (2013). Association between plasma PFOA and PFOS levels and total cholesterol in a middle-aged Danish population. *PloS one* 8(2): e56969.

Eriksen KT, Sorensen M, McLaughlin JK, et al. (2009). Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. *J Natl Cancer Inst* 101(8): 605-609.

Ernst A, Brix N, Lauridsen LLB, et al. (2019). Exposure to perfluoroalkyl substances during fetal life and pubertal development in boys and girls from the Danish National Birth Cohort. *Environmental health perspectives* 127(01): 017004.

Ernster VL (1994). Nested Case-Control Studies. *Preventive Medicine* 23(5): 587-590.

Family L, Zheng G, Cabezas M, et al. (2019). Reasons why low-income people in urban areas do not drink tap water. *The Journal of the American Dental Association* 150(6): 503-513.

Fan H, Ducatman A, Zhang J (2014). Perfluorocarbons and Gilbert syndrome (phenotype) in the C8 Health Study Population. *Environ Res* 135: 70-75.

Fassler CS, Pinney SE, Xie C, Biro FM, Pinney SM (2019). Complex relationships between perfluorooctanoate, body mass index, insulin resistance and serum lipids in young girls. *Environ Res* 176: 108558.

Fei C, McLaughlin JK, Lipworth L, Olsen J (2010). Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding. *Scandinavian journal of work, environment & health*: 413-421.

Filgo AJ, Quist EM, Hoenerhoff MJ, Brix AE, Kissling GE and Fenton SE (2015). Perfluorooctanoic Acid (PFOA)-induced Liver Lesions in Two Strains of Mice Following Developmental Exposures: PPARalpha Is Not Required. *Toxicol Pathol* 43(4): 558-568.

Fisher M, Arbuckle TE, Wade M, Haines DA (2013). Do perfluoroalkyl substances affect metabolic function and plasma lipids?--Analysis of the 2007-2009, Canadian Health Measures Survey (CHMS) Cycle 1. *Environ Res* 121: 95-103.

Foreman JE, Koga T, Kosyk O, et al. (2021a). Diminished Hepatocarcinogenesis by a Potent, High-Affinity Human PPARα Agonist in PPARA-Humanized Mice. *Toxicological Sciences* 183(1): 70-80.

Foreman JE, Koga T, Kosyk O, et al. (2021b). Species Differences between mouse and human pparα in modulating the hepatocarcinogenic effects of perinatal exposure to a high-affinity human PPARα agonist in mice. *Toxicological Sciences* 183(1): 81-92.

Fragki S, Dirven H, Fletcher T, et al. (2021). Systemic PFOS and PFOA exposure and disturbed lipid homeostasis in humans: what do we know and what not? *Crit Rev Toxicol* 51(2): 141-164.

Franko J, Meade BJ, Frasch HF, Barbero AM and Anderson SE (2012). Dermal penetration potential of perfluorooctanoic acid (PFOA) in human and mouse skin. *J Toxicol Environ Health A* 75(1): 50-62.

Frisbee SJ, Brooks Jr AP, Maher A, et al. (2009). The C8 health project: design, methods, and participants. *Environmental health perspectives* 117(12): 1873-1882.

Frisbee SJ, Shankar A, Knox SS, et al. (2010). Perfluorooctanoic Acid, Perfluorooctanesulfonate, and Serum Lipids in Children and Adolescents: Results From the C8 Health Project. *Arch Pediatr Adolesc Med* 164(9): 860-869.

FSANZ (2017). Hazard assessment report – Perfluorooctane sulfonate (PFOS), Perfluorooctanoic acid (PFOA), Perfluorohexane sulfonate (PFHxS).

Fu Y, Wang T, Fu Q, Wang P, Lu Y (2014). Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population. *Ecotoxicology and environmental safety* 106: 246-252.

Gallo V, Leonardi G, Genser B, et al. (2012). Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environ Health Perspect* 120(5): 655-660.

Gao J, He J, Zhai Y, Wada T, Xie W (2009). The constitutive androstane receptor is an anti-obesity nuclear receptor that improves insulin sensitivity. *Journal of Biological Chemistry* 284(38): 25984-25992.

Gao X, Ni W, Zhu S, et al. (2021). Per- and polyfluoroalkyl substances exposure during pregnancy and adverse pregnancy and birth outcomes: A systematic review and meta-analysis. *Environ Res* 201: 111632.

Gardener H, Sun Q, Grandjean P (2021). PFAS concentration during pregnancy in relation to cardiometabolic health and birth outcomes. *Environ Res* 192: 110287.

Garnick L, Massarsky A, Mushnick A, et al. (2021). An evaluation of health-based federal and state PFOA drinking water guidelines in the United States. *Science of the Total Environment* 761: 144107.

Geiger SD, Xiao J, Ducatman A, et al. (2014). The association between PFOA, PFOS and serum lipid levels in adolescents. *Chemosphere* 98: 78-83.

Gianni ML, Bettinelli ME, Manfra P, et al. (2019). Breastfeeding difficulties and risk for early breastfeeding cessation. *Nutrients* 11(10): 2266.

Giannini EG, Testa R, Savarino V (2005). Liver enzyme alteration: a guide for clinicians. *Cmaj* 172(3): 367-379.

Gilliland FD, Mandel JS (1993). Mortality among employees of a perfluorooctanoic acid production plant. *Journal of Occupational Medicine*: 950-954.

Girardi P, Merler E (2019). A mortality study on male subjects exposed to polyfluoroalkyl acids with high internal dose of perfluorooctanoic acid. *Environ Res* 179(Pt A): 108743.

Gleason JA, Post GB, Fagliano JA (2015). Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007–2010. *Environmental research* 136: 8-14.

Glüge J, Scheringer M, Cousins IT, et al. (2020). An overview of the uses of per-and polyfluoroalkyl substances (PFAS). *Environmental Science: Processes & Impacts* 22(12): 2345-2373.

Gold LS, Sawyer CB, Magaw R, et al. (1984). A carcinogenic potency database of the standardized results of animal bioassays. *Environmental health perspectives* 58: 9-319.

Gomis MI, Vestergren R, MacLeod M, Mueller JF, Cousins IT (2017). Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. *Environment International* 108: 92-102.

Gonzalez FJ, Shah YM (2008). PPARα: mechanism of species differences and hepatocarcinogenesis of peroxisome proliferators. *Toxicology* 246(1): 2-8.

Goodman J, Lynch H (2017). Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. *Toxicology and Applied Pharmacology* 319: 39-46.

Goodrum PE, Anderson JK, Luz AL, Ansell GK (2021). Application of a framework for grouping and mixtures toxicity assessment of PFAS: a closer examination of dose-additivity approaches. *Toxicological Sciences* 179(2): 262-278.

Govarts E, Iszatt N, Trnovec T, et al. (2018). Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: pooled analysis of seven European birth cohorts. *Environment International* 115: 267-278.

Grandjean P, Andersen EW, Budtz-Jorgensen E, et al. (2012). Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA* 307(4): 391-397.

Grandjean P, Heilmann C, Weihe P, et al. (2017). Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. *J Immunotoxicol* 14(1): 188-195.

Greenland S, Senn SJ, Rothman KJ, et al. (2016). Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* 31(4): 337-350.

Grice MM, Alexander BH, Hoffbeck R, Kampa DM (2007). Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. *Journal of occupational and environmental medicine*: 722-729.

Griffith F, Long J (1980). Animal toxicity studies with ammonium perfluorooctanoate. *American Industrial Hygiene Association Journal* 41(8): 576-583.

Guo H, Wang J, Yao J, et al. (2019). Comparative hepatotoxicity of novel PFOA alternatives (perfluoropolyether carboxylic acids) on male mice. *Environmental science & technology* 53(7): 3929-3937.

Guruge KS, Hikono H, Shimada N, et al. (2009). Effect of perfluorooctane sulfonate (PFOS) on influenza A virus-induced mortality in female B6C3F1 mice. *The Journal of toxicological sciences* 34(6): 687-691.

Hall A, Elcombe C, Foster J, et al. (2012). Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP Expert Workshop. *Toxicologic pathology* 40(7): 971-994.

Han X, Meng L, Zhang G, et al. (2021). Exposure to novel and legacy per- and polyfluoroalkyl substances (PFASs) and associations with type 2 diabetes: A case-control study in East China. *Environ Int* 156: 106637.

Haug LS, Thomsen C, Becher G (2009). Time trends and the influence of age and gender on serum concentrations of perfluorinated compounds in archived human samples. *Environ Sci Technol* 43(6): 2131-2136.

Haughom B, Spydevold Ø (1992). The mechanism underlying the hypolipemic effect of perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibric acid. *Biochimica et biophysica acta (BBA)-lipids and lipid metabolism* 1128(1): 65-72.

Hays T, Rusyn I, Burns AM, et al. (2005). Role of peroxisome proliferator-activated receptor-α (PPARα) in bezafibrate-induced hepatocarcinogenesis and cholestasis. *Carcinogenesis* 26(1): 219-227.

Health Canada (2018). Guidelines for Canadian Drinking Water Quality. Guideline Technical Document – Perfluorooctane Sulfonate (PFOS). Ottawa, Ontario (December 2018).

Hill AB (1965). The environment and disease: association or causation? *Proc R Soc Med* 58: 295-300.

Hinderliter PM, Mylchreest E, Gannon SA, Butenhoff JL and Kennedy Jr GL (2005). Perfluorooctanoate: placental and lactational transport pharmacokinetics in rats. *Toxicology* 211(1-2): 139-148.

Hu J, Mao Y, White K, Canadian Cancer Registries Epidemiology Research G (2003). Overweight and obesity in adults and risk of renal cell carcinoma in Canada. *Soz Praventivmed* 48(3): 178-185.

Hu XC, Tokranov AK, Liddie J, et al. (2019). Tap water contributions to plasma concentrations of poly-and perfluoroalkyl substances (PFAS) in a nationwide prospective cohort of US women. *Environmental health perspectives* 127(6): 067006.

Hu Y, Liu G, Rood J, et al. (2019). Perfluoroalkyl substances and changes in bone mineral density: A prospective analysis in the POUNDS-LOST study. *Environ Res* 179(Pt A): 108775.

Huedo-Medina T, Sanchez-Meca J, Marin-Martinez F, Botella J (2006). Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *CHIP documents* 6-1-2006.

Hui S, Slemenda C, Johnston C (1990). The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis international* 1(1): 30-34.

Hui Z, Li R, Chen L (2017). The impact of exposure to environmental contaminant on hepatocellular lipid metabolism. *Gene* 622: 67-71.

Hundley S, Sarrif A, Kennedy Jr G (2006). Absorption, distribution, and excretion of ammonium perfluorooctanoate (APFO) after oral administration to various species. *Drug and chemical toxicology* 29(2): 137-145.

Huo X, Huang R, Gan Y, et al. (2020). Perfluoroalkyl substances in early pregnancy and risk of hypertensive disorders of pregnancy: a prospective cohort study. *Environment International* 138: 105656.

IARC (2012). Arsenic, Metals, Fibres, and Dusts. IARC Monographs on the evaluation of carcinogenic risks to humans, International Agency for Research on Cancer. 100C.

IARC (2017). Some chemicals used as solvents and in polymer manufacture. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 110.

IARC (2019). IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Preamble. International Agency for Research on Cancer.

Ito Y, Yamanoshita O, Asaeda N, et al. (2007). Di(2-ethylhexyl)phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor alpha-independent pathway. *J Occup Health* 49(3): 172-182.

Jain RB (2019). Concentration of selected liver enzymes across the stages of glomerular function: the associations with PFOA and PFOS. *Heliyon* 5(7): e02168.

Jain RB, Ducatman A (2019). Selective Associations of Recent Low Concentrations of Perfluoroalkyl Substances With Liver Function Biomarkers: NHANES 2011 to 2014 Data on US Adults Aged >/=20 Years. *J Occup Environ Med* 61(4): 293-302.

Jeddy Z, Tobias JH, Taylor EV, et al. (2018). Prenatal concentrations of perfluoroalkyl substances and bone health in British girls at age 17. *Archives of osteoporosis* 13(1): 1-7.

Jensen RC, Andersen MS, Larsen PV, et al. (2020). Prenatal Exposures to Perfluoroalkyl Acids and Associations with Markers of Adiposity and Plasma Lipids in Infancy: An Odense Child Cohort Study. *Environ Health Perspect* 128(7): 77001.

Ji J, Song L, Wang J, et al. (2021). Association between urinary per- and poly-fluoroalkyl substances and COVID-19 susceptibility. *Environ Int* 153: 106524.

Jiang W, Deng Y, Song Z, et al. (2020). Gestational perfluorooctanoic acid exposure inhibits placental development by dysregulation of labyrinth vessels and uNK cells and apoptosis in mice. *Frontiers in Physiology* 11: 51.

Jin R, McConnell R, Catherine C, et al. (2020). Perfluoroalkyl substances and severity of nonalcoholic fatty liver in Children: An untargeted metabolomics approach. *Environ Int* 134: 105220.

Johnston J, Cushing L (2020). Chemical exposures, health, and environmental justice in communities living on the fenceline of industry. *Current environmental health reports* 7(1): 48-57.

Kale A, Deardorff J, Lahiff M, et al. (2015). Breastfeeding versus formula-feeding and girls' pubertal development. *Maternal and child health journal* 19(3): 519-527.

Karami S, Boffetta P, Stewart PS, et al. (2011). Occupational exposure to dusts and risk of renal cell carcinoma. *Br J Cancer* 104(11): 1797-1803.

Kasarala G, Tillmann HL (2016). Standard liver tests. *Clinical Liver Disease* 8(1): 13.

Kato K, Wong LY, Jia LT, Kuklenyik Z, Calafat AM (2011). Trends in exposure to polyfluoroalkyl chemicals in the U.S. Population: 1999-2008. *Environ Sci Technol* 45(19): 8037-8045.

Kennedy GL, Butenhoff JL, Olsen GW, et al. (2004). The toxicology of perfluorooctanoate. *Critical reviews in toxicology* 34(4): 351-384.

Kennedy Jr G, Hall G, Brittelli M, Barnes J, Chen H (1986). Inhalation toxicity of ammonium perfluorooctanoate. *Food and chemical toxicology* 24(12): 1325-1329.

Khalil N, Chen A, Lee M, et al. (2016). Association of Perfluoroalkyl Substances, Bone Mineral Density, and Osteoporosis in the U.S. Population in NHANES 2009-2010. *Environ Health Perspect* 124(1): 81-87.

Khalil N, Ebert JR, Honda M, et al. (2018). Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8-12 year old children: A pilot study. *Environ Res* 160: 314-321.

Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC, Disease PPCotAAftSoL (2008). Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *HEPATOLOGY-BALTIMORE THEN ORLANDO-* 47(4): 1363.

Kimura O, Fujii Y, Haraguchi K, et al. (2017). Uptake of perfluorooctanoic acid by Caco-2 cells: Involvement of organic anion transporting polypeptides. *Toxicology letters* 277: 18-23.

Kirk AB, Michelsen-Correa S, Rosen C, Martin CF, Blumberg B (2021). PFAS and Potential Adverse Effects on Bone and Adipose Tissue Through Interactions With PPARgamma. *Endocrinology* 162(12).

Klaunig JE, Hocevar BA, Kamendulis LM (2012). Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance. *Reproductive toxicology* 33(4): 410-418.

Klibanski A, Adams-Campbell L, Bassford T, et al. (2001). Osteoporosis prevention, diagnosis, and therapy. *Journal of the American Medical Association* 285(6): 785-795.

Knutsen HK, Alexander J, Barregård L, et al. (2018). Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA Panel on Contaminants in the Food Chain. *EFSA Journal* 16(12): e05194.

Koskela A, Finnilä M, Korkalainen M, et al. (2016). Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. *Toxicology and Applied Pharmacology* 301: 14-21.

Koskela A, Koponen J, Lehenkari P, et al. (2017). Perfluoroalkyl substances in human bone: concentrations in bones and effects on bone cell differentiation. *Scientific reports* 7(1): 1-9.

Kristensen S, Ramlau-Hansen C, Ernst E, et al. (2013). Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. *Human reproduction* 28(12): 3337-3348.

Kudo N, Mizuguchi H, Yamamoto A, Kawashima Y (1999). Alterations by perfluorooctanoic acid of glycerolipid metabolism in rat liver. *Chemico-biological interactions* 118(1): 69-83.

Kwiatkowski CF, Andrews DQ, Birnbaum LS, et al. (2020). Scientific basis for managing PFAS as a chemical class. *Environmental science & technology letters* 7(8): 532-543.

Lake B (2009). Species differences in the hepatic effects of inducers of CYP2B and CYP4A subfamily forms: relationship to rodent liver tumour formation. *Xenobiotica* 39(8): 582-596.

Lang JM, Rothman KJ, Cann CI (1998). That confounded P-value. Epidemiology 9(1): 7-8.

Lau C, Thibodeaux JR, Hanson RG, et al. (2006). Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. *Toxicological Sciences* 90(2): 510-518.

Lechosa-Muñiz C, Paz-Zulueta M, Cayón-De las Cuevas J, Llorca J, Cabero-Pérez MJ (2021). Declared Reasons for Cessation of Breastfeeding during the First Year of Life: An Analysis Based on a Cohort Study in Northern Spain. *International Journal of Environmental Research and Public Health* 18(16): 8414.

Leek JT, Peng RD (2015). P values are just the tip of the iceberg. Nature 520: 612.

Leonard RC, Kreckmann KH, Sakr CJ, Symons JM (2008). Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. *Annals of Epidemiology* 18(1): 15-22.

Li F, Duan J, Tian S, et al. (2020b). Short-chain per-and polyfluoroalkyl substances in aquatic systems: Occurrence, impacts and treatment. *Chemical Engineering Journal* 380: 122506.

Li H, Hammarstrand S, Midberg B, et al. (2022). Cancer incidence in a Swedish cohort with high exposure to perfluoroalkyl substances in drinking water. *Environ Res* 204(Pt C): 112217.

Li J, Quan X, Lei S, et al. (2022). LncRNA MEG3 alleviates PFOS induced placental cell growth inhibition through its derived miR-770 targeting PTX3. *Environmental pollution* 293: 118542.

Li J, Quan X, Lei S, et al. (2021). PFOS Inhibited Normal Functional Development of Placenta Cells via PPARγ Signaling. *Biomedicines* 9(6): 677.

Li J, Yao J, Xia W, et al. (2020). Association between exposure to per- and polyfluoroalkyl substances and blood glucose in pregnant women. *Int J Hyg Environ Health* 230: 113596.

Li N, Liu Y, Papandonatos GD, et al. (2021). Gestational and childhood exposure to per- and polyfluoroalkyl substances and cardiometabolic risk at age 12 years. *Environ Int* 147: 106344.

Li Y, Barregard L, Xu Y, et al. (2020a). Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. *Environ Health* 19: 1-11.

Li Y, Fletcher T, Mucs D, et al. (2018). Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occupational and environmental medicine* 75(1): 46-51.

Lin C-Y, Lin L-Y, Chiang C-K, et al. (2010). Investigation of the associations between low-dose serum perfluorinated chemicals and liver enzymes in US adults. *Official journal of the American College of Gastroenterology| ACG* 105(6): 1354-1363.

Lin LY, Wen LL, Su TC, Chen PC, Lin CY (2014). Negative association between serum perfluorooctane sulfate concentration and bone mineral density in US premenopausal women: NHANES, 2005-2008. *J Clin Endocrinol Metab* 99(6): 2173-2180.

Lin PD, Cardenas A, Hauser R, et al. (2019). Per- and polyfluoroalkyl substances and blood lipid levels in pre-diabetic adults-longitudinal analysis of the diabetes prevention program outcomes study. *Environ Int* 129: 343-353.

Lin TW, Chen MK, Lin CC, et al. (2020). Association between exposure to perfluoroalkyl substances and metabolic syndrome and related outcomes among older residents living near a Science Park in Taiwan. *Int J Hyg Environ Health* 230: 113607.

Loccisano AE, Campbell Jr JL, Butenhoff JL, Andersen ME, Clewell III HJ (2012). Comparison and evaluation of pharmacokinetics of PFOA and PFOS in the adult rat using a physiologically based pharmacokinetic model. *Reproductive toxicology* 33(4): 452-467.

Lopez-Espinosa M-J, Fletcher T, Armstrong B, et al. (2011). Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant. *Environmental science & technology* 45(19): 8160-8166.

Lorber M, Egeghy PP (2011). Simple intake and pharmacokinetic modeling to characterize exposure of Americans to perfluoroctanoic acid, PFOA. *Environmental science & technology* 45(19): 8006-8014.

Lou I, Wambaugh JF, Lau C, et al. (2009). Modeling single and repeated dose pharmacokinetics of PFOA in mice. *Toxicological Sciences* 107(2): 331-341.

Loveless SE, Finlay C, Everds NE, et al. (2006). Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). *Toxicology* 220(2-3): 203-217.

Loveless SE, Hoban D, Sykes G, Frame SR, Everds NE (2008). Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. *Toxicological Sciences* 105(1): 86-96.

Luebker DJ, Hansen KJ, Bass NM, Butenhoff JL, Seacat AM (2002). Interactions of flurochemicals with rat liver fatty acid-binding protein. *Toxicology* 176(3): 175-185.

Lum KJ, Sundaram R, Barr DB, Louis TA, Louis GMB (2017). Perfluoroalkyl chemicals, menstrual cycle length, and fecundity: Findings from a prospective pregnancy study. *Epidemiology (Cambridge, Mass.)* 28(1): 90.

Lundin JI, Alexander BH, Olsen GW, Church TR (2009). Ammonium perfluorooctanoate production and occupational mortality. *Epidemiology*: 921-928.

Luo Y, Deji Z, Huang Z (2020). Exposure to perfluoroalkyl substances and allergic outcomes in children: A systematic review and meta-analysis. *Environ Res* 191: 110145.

Macon MB, Villanueva LR, Tatum-Gibbs K, et al. (2011). Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. *Toxicological Sciences* 122(1): 134-145.

Mancini FR, Cano-Sancho G, Gambaretti J, et al. (2020). Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case-control study in the French E3N cohort. *International Journal of Cancer* 146(4): 917-928.

Manzano-Salgado CB, Granum B, Lopez-Espinosa MJ, et al. (2019). Prenatal exposure to perfluoroalkyl substances, immune-related outcomes, and lung function in children from a Spanish birth cohort study. *Int J Hyg Environ Health* 222(6): 945-954.

Mastrantonio M, Bai E, Uccelli R, et al. (2018). Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. *The European Journal of Public Health* 28(1): 180-185.

Mattsson K, Rignell-Hydbom A, Holmberg S, et al. (2015). Levels of perfluoroalkyl substances and risk of coronary heart disease: Findings from a population-based longitudinal study. *Environ Res* 142: 148-154.

McConnell EE, Solleveld HA, Swenberg JA, Boorman GA (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *Journal of the National Cancer Institute* 76(2): 283-289.

Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH (1994). Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. *Cancer Causes Control* 5(2): 105-113.

Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS (2010). Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the US National Health and Nutrition Examination Survey. *Environmental health perspectives* 118(5): 686-692.

Miller MD, Crofton KM, Rice DC, Zoeller RT (2009). Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. *Environ Health Perspect* 117(7): 1033-1041.

Minata M, Harada KH, Kärrman A, et al. (2010). Role of peroxisome proliferator-activated receptor-α in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver. *Industrial health* 48(1): 96-107.

Mitro SD, Sagiv SK, Fleisch AF, et al. (2020). Pregnancy Per- and Polyfluoroalkyl Substance Concentrations and Postpartum Health in Project Viva: A Prospective Cohort. *J Clin Endocrinol Metab* 105(9).

MNDOH (2020a). Toxicological Summary for: Perfluorooctanoate. Minnesota Department of Health.

MNDOH (2020b). Toxicological Summary for: Perfluorooctane sulfonate. Minnesota Department of Health.

Morimura K, Cheung C, Ward JM, Reddy JK, Gonzalez FJ (2006). Differential susceptibility of mice humanized for peroxisome proliferator-activated receptor α to Wy-14,643-induced liver tumorigenesis. *Carcinogenesis* 27(5): 1074-1080.

Muscat JE, Hoffmann D, Wynder EL (1995). The epidemiology of renal cell carcinoma. A second look. *Cancer* 75(10): 2552-2557.

Myer JR, Romach EH, Elangbam CS (2014). Species-and Dose-specific pancreatic responses and progression in single-and repeat-dose studies with GI181771X: a novel cholecystokinin 1 receptor agonist in mice, rats, and monkeys. *Toxicologic pathology* 42(1): 260-274.

Nakagawa T, Ramdhan DH, Tanaka N, et al. (2012). Modulation of ammonium perfluorooctanoate-induced hepatic damage by genetically different PPARα in mice. *Archives of toxicology* 86(1): 63-74.

Nakamura T, Ito Y, Yanagiba Y, et al. (2009). Microgram-order ammonium perfluorooctanoate may activate mouse peroxisome proliferator-activated receptor α, but not human PPARα. *Toxicology* 265(1-2): 27-33.

NASEM (2019). A Class Approach to Hazard Assessment of Organohalogen Flame Retardants. National Academies of Sciences, Engineering, and Medicine. Washington, DC: The National Academies Press. doi:doi:10.17226/25412.

Negro R, Soldin OP, Obregon M-J, Stagnaro-Green A (2011). Hypothyroxinemia and pregnancy. *Endocrine Practice* 17(3): 422-429.

Nelson JW, Hatch EE, Webster TF (2010). Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general US population. *Environ Health Perspect* 118(2): 197-202.

Nelson JW, Scammell MK, Hatch EE, Webster TF (2012). Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003-2006. *Environ Health* 11: 10.

Newsome PN, Cramb R, Davison SM, et al. (2018). Guidelines on the management of abnormal liver blood tests. *Gut* 67(1): 6-19.

NHANES (2022). "NHANES 2017-2018 Laboratory Data." NHANES 2017-2018 Laboratory Data [accessed 05/09/2022.

NHDES (2019). Rules Related to Per- and Polyfluoroalkyl Substances (PFAS): FP 2019-14, Env-Wq 402 amendments; FP 2019-15, Env-Or 603.03 amendments; FP 2019-16, Env-Dw 700-800 amendments. Summary of Comments on Initial Proposals with NHDES Responses, June 28, 2019. 104.

Nielsen G, Heiger-Bernays WJ, Schlezinger JJ, Webster TF (2022). Predicting the effects of per-and polyfluoroalkyl substance mixtures on peroxisome proliferator-activated receptor alpha activity in vitro. *Toxicology* 465: 153024.

NJDEP (2019a). Technical Support Document: Interim Specific Ground Water Criterion for Perfluorooctanoic Acid (PFOA, C8). Division of Science, Research & Environmental Health, New Jersey Department of Environmental Protection.

NJDEP (2019b). Technical Support Document: Interim Specific Ground Water Criterion for Perfluorooctane Sulfonate (PFOS). Division of Science, Research and Environmental Health, New Jersey Department of Environmental Protection.

NTP (2016). Systematic Review of Immunotoxicity associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS). National Toxicology Program, U.S. Department of Health and Human Services. Research Triangle Park, North Carolina,

NTP (2019a). Toxicity studies of perfluoroalkyl carboxylates administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) Rats. In Toxicity report series (Issue 97). https://doi.org/10.22427/NTP-TOX-97. National Toxicology Program.

NTP (2019b). TR-598: Technical Report Pathology Tables and Curves - PFOA. Research Triangle Park, North Carolina, National Toxicology Program.

NTP (2020). NTP technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid (CASRN 335-67-1) administered in feed to Sprague Dawley (Hsd: Sprague Dawley® SD®) rats. National Toxicology Program.

Obourn JD, Frame SR, Bell Jr RH, et al. (1997). Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicology and Applied Pharmacology* 145(2): 425-436.

OECD (2021). Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance. OECD Series on Risk Management, No. 61. OECD Publishing: Paris, France.

OEHHA (2004). Public Health Goals for Chemicals in Drinking Water: Arsenic. *Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.*

OEHHA (2008). Air toxics hot spots risk assessment guidelines: Technical support document for the derivation of noncancer reference exposure levels. *Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.*

OEHHA (2009). Technical support document for cancer potency factors: methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. *Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.*

OEHHA (2012). Air Toxics Hot Spots Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis, Chapter 8. Sacramento, CA, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

OEHHA (2021). Proposition 65 Carcinogen Identification Committee - December 6, 2021. https://oehha.ca.gov/media/downloads/crnr/120621cictranscript.pdf

Olsen GW (2018). Re: Health Status of Workers Exposed to Perfluorinated Alkylate Substances. *Journal of occupational and environmental medicine* 60(10): e563-e566.

Olsen GW, Burris JM, Burlew MM, Mandel JH (2000). Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug and chemical toxicology* 23(4): 603-620.

Olsen GW, Burris JM, Ehresman DJ, et al. (2007). Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environmental health perspectives* 115(9): 1298-1305.

Olsen GW, Huang HY, Helzlsouer KJ, et al. (2005). Historical comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in human blood. *Environ Health Perspect* 113(5): 539-545.

Olsen GW, Zobel LR (2007). Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. *International archives of occupational and environmental health* 81(2): 231-246.

Peng S, Yan L, Zhang J, et al. (2013). An integrated metabonomics and transcriptomics approach to understanding metabolic pathway disturbance induced by perfluorooctanoic acid. *Journal of pharmaceutical and biomedical analysis* 86: 56-64.

Pinney SM, Biro FM, Windham GC, et al. (2014). Serum biomarkers of polyfluoroalkyl compound exposure in young girls in Greater Cincinnati and the San Francisco Bay Area, USA. *Environmental pollution* 184: 327-334.

Pizzurro DM, Seeley M, Kerper LE, Beck BD (2019). Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria. *Regulatory Toxicology and Pharmacology* 106: 239-250.

Post GB (2021). Recent US State and Federal Drinking Water Guidelines for Per- and Polyfluoroalkyl Substances. *Environmental Toxicology and Chemistry* 40(3): 550-563.

Pouwer MG, Pieterman EJ, Chang S-C, et al. (2019). Dose effects of ammonium perfluorooctanoate on lipoprotein metabolism in APOE* 3-Leiden. CETP mice. *Toxicological Sciences* 168(2): 519-534.

Preston EV, Rifas-Shiman SL, Hivert MF, et al. (2020). Associations of Per- and Polyfluoroalkyl Substances (PFAS) With Glucose Tolerance During Pregnancy in Project Viva. *J Clin Endocrinol Metab* 105(8).

Qazi MR, Abedi MR, Nelson BD, DePierre JW, Abedi-Valugerdi M (2010). Dietary exposure to perfluorooctanoate or perfluorooctane sulfonate induces hypertrophy in centrilobular hepatocytes and alters the hepatic immune status in mice. *International immunopharmacology* 10(11): 1420-1427.

Rahman ML, Zhang C, Smarr MM, et al. (2019). Persistent organic pollutants and gestational diabetes: A multi-center prospective cohort study of healthy US women. *Environ Int* 124: 249-258.

Raleigh KK, Alexander BH, Olsen GW, et al. (2014). Mortality and cancer incidence in ammonium perfluorooctanoate production workers. *Occupational and environmental medicine* 71(7): 500-506.

Rana S, Lemoine E, Granger JP, Karumanchi SA (2019). Preeclampsia: pathophysiology, challenges, and perspectives. *Circulation research* 124(7): 1094-1112.

Rantakokko P, Mannisto V, Airaksinen R, et al. (2015). Persistent organic pollutants and non-alcoholic fatty liver disease in morbidly obese patients: a cohort study. *Environ Health* 14: 79.

Rebholz SL, Jones T, Herrick RL, et al. (2016). Hypercholesterolemia with consumption of PFOA-laced Western diets is dependent on strain and sex of mice. *Toxicology reports* 3: 46-54.

Ren Y, Jin L, Yang F, et al. (2020). Concentrations of perfluoroalkyl and polyfluoroalkyl substances and blood glucose in pregnant women. *Environ Health* 19(1): 88.

Rhee J, Chang VC, Cheng I, et al. (2023). Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma in the Multiethnic Cohort Study. Environ Int. 180:108197

Rosen MB, Das KP, Wood CR, et al. (2013). Evaluation of perfluoroalkyl acid activity using primary mouse and human hepatocytes. *Toxicology* 308: 129-137.

Ross J, Plummer SM, Rode A, et al. (2010). Human constitutive androstane receptor (CAR) and pregnane X receptor (PXR) support the hypertrophic but not the hyperplastic response to the murine nongenotoxic hepatocarcinogens phenobarbital and chlordane in vivo. *Toxicological Sciences* 116(2): 452-466.

Rothman KJ (1990). No adjustments are needed for multiple comparisons. *Epidemiology* 1(1): 43-46.

Rothman KJ, Greenland S, Lash TL. (2008). *Modern epidemiology*, Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia.

Rowan-Carroll A, Reardon A, Leingartner K, et al. (2021). High-throughput transcriptomic analysis of human primary hepatocyte spheroids exposed to per-and polyfluoroalkyl substances as a platform for relative potency characterization. *Toxicological Sciences* 181(2): 199-214.

Rylander L, Lindh CH, Hansson SR, Broberg K, Källén K (2020). Per-and polyfluoroalkyl substances in early pregnancy and risk for preeclampsia: A case-control study in Southern Sweden. *Toxics* 8(2): 43.

Sakr CJ, Kreckmann KH, Green JW, et al. (2007a). Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate

or APFO) as part of a general health survey in a cohort of occupationally exposed workers. *J Occup Environ Med* 49(10): 1086-1096.

Sakr CJ, Leonard RC, Kreckmann KH, Slade MD, Cullen MR (2007b). Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. *Journal of occupational and environmental medicine*: 872-879.

Salihovic S, Dickens AM, Schoultz I, et al. (2020). Simultaneous determination of perfluoroalkyl substances and bile acids in human serum using ultra-high-performance liquid chromatography-tandem mass spectrometry. *Anal Bioanal Chem* 412(10): 2251-2259.

Salihovic S, Lind L, Larsson A, Lind PM (2020). Plasma perfluoroalkyls are associated with decreased levels of proteomic inflammatory markers in a cross-sectional study of an elderly population. *Environment International* 145: 106099.

Savitz DA (2013). Commentary: Reconciling Theory and PracticeWhat Is to Be Done with P Values? *Epidemiology* 24(2): 212-214.

Schecter A, Malik-Bass N, Calafat AM, et al. (2012). Polyfluoroalkyl compounds in Texas children from birth through 12 years of age. *Environmental health perspectives* 120(4): 590-594.

Schillemans T, Donat-Vargas C, Lindh CH, et al. (2022). Per- and Polyfluoroalkyl Substances and Risk of Myocardial Infarction and Stroke: A Nested Case-Control Study in Sweden. Environ Health Perspect. 130(3):37007

Schlezinger J, Hyötyläinen T, Sinioja T, et al. (2021). Perfluorooctanoic acid induces liver and serum dyslipidemia in humanized pparα mice fed an american diet. *Toxicology and Applied Pharmacology* 426: 115644.

Schlezinger J, Puckett H, Oliver J, et al. (2020). Perfluorooctanoic acid activates multiple nuclear receptor pathways and skews expression of genes regulating cholesterol homeostasis in liver of humanized PPARα mice fed an American diet. *Toxicology and Applied Pharmacology* 405: 115204.

Schrenk D, Bignami M, Bodin L, et al. (2020). Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA Journal* 18(9): e06223.

Seals R, Bartell SM, Steenland K (2011). Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. *Environmental health perspectives* 119(1): 119-124.

Semenza JC, Ziogas A, Largent J, Peel D, Anton-Culver H (2001). Gene-environment interactions in renal cell carcinoma. *Am J Epidemiol* 153(9): 851-859.

Shearer JJ, Callahan CL, Calafat AM, et al. (2021). Serum concentrations of per-and polyfluoroalkyl substances and risk of renal cell carcinoma. *J Natl Cancer Inst* 113(5): 580-587.

Shih YH, Blomberg AJ, Bind MA, et al. (2021). Serum vaccine antibody concentrations in adults exposed to per- and polyfluoroalkyl substances: A birth cohort in the Faroe Islands. *J Immunotoxicol* 18(1): 85-92.

Shin HM, Vieira VM, Ryan PB, Steenland K, Bartell SM (2011). Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project. Environ Health Perspect 119(12): 1760-1765.

Skuladottir M, Ramel A, Rytter D, et al. (2015). Examining confounding by diet in the association between perfluoroalkyl acids and serum cholesterol in pregnancy. *Environ Res* 143(Pt A): 33-38.

Smith MT, Guyton KZ, Gibbons CF, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environmental health perspectives* 124(6): 713-721.

Sobus JR, DeWoskin RS, Tan YM, et al. (2015). Uses of NHANES Biomarker Data for Chemical Risk Assessment: Trends, Challenges, and Opportunities. *Environ Health Perspect* 123(10): 919-927.

Spruiell K, Richardson RM, Cullen JM, et al. (2014). Role of pregnane X receptor in obesity and glucose homeostasis in male mice. *Journal of Biological Chemistry* 289(6): 3244-3261.

Starling AP, Engel SM, Whitworth KW, et al. (2014). Perfluoroalkyl substances and lipid concentrations in plasma during pregnancy among women in the Norwegian Mother and Child Cohort Study. *Environment International* 62: 104-112.

Steenland K, Barry V, Savitz D (2018). Serum Perfluorooctanoic Acid and Birthweight: An Updated Meta-analysis With Bias Analysis. *Epidemiology* 29(6): 765-776.

Steenland K, Fletcher T, Stein CR, et al. (2020). Evolution of evidence on PFOA and health following the assessments of the C8 Science Panel. *Environment International* 145: 106125.

Steenland K, Jin C, MacNeil J, et al. (2009a). Predictors of PFOA levels in a community surrounding a chemical plant. *Environmental health perspectives* 117(7): 1083-1088.

Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V (2009b). Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *Am J Epidemiol* 170(10): 1268-1278.

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

Steenland K, Woskie S (2012). Cohort mortality study of workers exposed to perfluorooctanoic acid. *American journal of epidemiology* 176(10): 909-917.

Stein CR, Ge Y, Wolff MS, et al. (2016). Perfluoroalkyl substance serum concentrations and immune response to FluMist vaccination among healthy adults. *Environmental research* 149: 171-178.

Sterne JA, Davey Smith G (2001). Sifting the evidence-what's wrong with significance tests? BMJ 322(7280): 226-231.

Sterne JA, Gavaghan D, Egger M (2000). Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 53(11): 1119-1129.

Stuebe AM, Horton BJ, Chetwynd E, et al. (2014). Prevalence and risk factors for early, undesired weaning attributed to lactation dysfunction. *Journal of Women's Health* 23(5): 404-412.

Su S, Billy LJ, Chang S, et al. (2022). The role of mouse and human peroxisome proliferator-activated receptor-α in modulating the hepatic effects of perfluorooctane sulfonate in mice. *Toxicology* 465: 153056.

Sunderland EM, Hu XC, Dassuncao C, et al. (2019). A review of the pathways of human exposure to poly-and perfluoroalkyl substances (PFASs) and present understanding of health effects. *Journal of exposure science & environmental epidemiology* 29(2): 131-147.

Suzuki H, Mohr U, Kimmerle G (1979). Spontaneous endocrine tumors in Sprague-Dawley rats. *Journal of Cancer Research and Clinical Oncology* 95(2): 187-196.

Tardiff RG (2009). Comment on “Occurrence and potential significance of perfluorooctanoic acid (PFOA) detected in New Jersey public drinking water systems”. *Environmental science & technology* 43(22): 8701-8701.

Temkin AM, Hocevar BA, Andrews DQ, Naidenko OV, Kamendulis LM (2020). Application of the key characteristics of carcinogens to per and polyfluoroalkyl substances. *International Journal of Environmental Research and Public Health* 17(5): 1668.

Thomford PJ (2002). 104-Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Rats. 3M T-6295. Madison, WI, Covance Laboratories.

Timmermann CAG, Andersen MS, Budtz-Jørgensen E, et al. (2022). Pregnancy Exposure to Perfluoroalkyl Substances and Associations With Prolactin Concentrations and Breastfeeding in the Odense Child Cohort. *The Journal of Clinical Endocrinology & Metabolism* 107(2): e631-e642.

Timmermann CAG, Budtz-Jørgensen E, Petersen MS, et al. (2017). Shorter duration of breastfeeding at elevated exposures to perfluoroalkyl substances. *Reproductive toxicology* 68: 164-170.

Timmermann CAG, Jensen KJ, Nielsen F, et al. (2020). Serum Perfluoroalkyl Substances, Vaccine Responses, and Morbidity in a Cohort of Guinea-Bissau Children. *Environ Health Perspect* 128(8): 87002.

Timmermann CAG, Pedersen HS, Weihe P, et al. (2022). Concentrations of tetanus and diphtheria antibodies in vaccinated Greenlandic children aged 7-12 years exposed to marine pollutants, a cross sectional study. Environ Res. 203:111712

Tindle HA, Stevenson Duncan M, Greevy RA, et al. (2018). Lifetime smoking history and risk of lung cancer: results from the Framingham Heart Study. *JNCI: Journal of the National Cancer Institute* 110(11): 1201-1207.

Torres L, Redko A, Limper C, et al. (2021). Effect of Perfluorooctanesulfonic acid (PFOS) on immune cell development and function in mice. *Immunology Letters* 233: 31-41.

Trowbridge J, Gerona RR, Lin T, et al. (2020). Exposure to perfluoroalkyl substances in a cohort of women firefighters and office workers in San Francisco. *Environmental science & technology* 54(6): 3363-3374.

Trudel D, Horowitz L, Wormuth M, et al. (2008). Estimating consumer exposure to PFOS and PFOA. *Risk Analysis: An International Journal* 28(2): 251-269.

Tsai MS, Chang SH, Kuo WH, et al. (2020). A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. *Environ Int* 142: 105850.

Tucker DK, Macon MB, Strynar MJ, et al. (2015). The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. *Reproductive toxicology* 54: 26-36.

Ubel F, Sorenson S, Roach D (1980). Health status of plant workers exposed to fluorochemicals-a preliminary report. *American Industrial Hygiene Association Journal* 41(8): 584-589.

US Census Bureau (2018). "U.S. Population Up 5.96% Since 2010." https://www.census.gov/library/visualizations/interactive/population-increase-2018.html.

US EPA (2000). Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health.

US EPA (2003). Proposed OPPTS Science Policy: PPARα-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments. Office of Prevention, Pesticides & Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

US EPA (2005). Guidelines for Carcinogen Risk Assessment. Washington DC. https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

US EPA (2011). Toxicological Review of Trichloroethylene. Integrated Risk Information System (IRIS).

US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC, United States Environmental Protection Agency.

US EPA (2014). Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Interspecies Extrapolation. Washington, DC: Office of the Science Advisor U.S. Environmental Protection Agency (EPA/R-14/002F).

US EPA (2016a). "Health Effects Support Document for Perfluorooctanoic Acid (PFOA). EPA Document Number: 822-R-16-003." https://www.epa.gov/sites/default/files/2016-05/documents/pfoa_hesd_final-plain.pdf [accessed 02/03/22.

US EPA (2016b). "Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). EPA Document Number: 822-R-16-002." https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf [accessed 02/03/22.

US EPA (2017). Evaluation of the Carcinogeneic Potential of Novilflumuron (XDE-007). Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs. U. S. Environmental Protection Agency.

US EPA (2018a). Public Review Draft: Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3). EPA 823P18001. U.S. Environmental Protection Agency, Washington, DC.

US EPA (2018b). 2018 Edition of the Drinking Water Standards and Health Advisories Tables. U.S. Environmental Protection Agency, Washington, DC.

US EPA (2018c). Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). EPA/635/R-18/211Fa. U. S. Environmental Protection agency.

US EPA (2019a). OLEM Directive No. 9283.1-47. Memorandum Subject: Interim Recommendations to Address Groundwater Contaminated with Perfluorooctanoic Acid

and Perfluorooctanesulfonate. Office of Land and Emergency Management, U. S. Environemental Protection Agency. Washington, DC.

US EPA (2019b). Update for Chapter 3 of the Exposure Factors Handbook. Ingestion of Water and Other Liquids. EPA/600/R-18/259F U. S. Environemental Protection Agency. Washington, DC.

US EPA (2021a). External Peer Review Draft. Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) (CASRN 335-67-1) in Drinking Water. EPA document No. 822D21001. U.S. Environmental Protection Agency Office of Water (4304T) Health and Ecological Criteria Division, Washington, DC 20460.

US EPA (2021b). External Peer Review Draft. Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) (CASRN 1763-23-1) in Drinking Water. EPA document No. 822D21002. U.S. Environmental Protection Agency Office of Water (4304T) Health and Ecological Criteria Division, Washington, DC 20460.

US EPA (2021c). PFAS Strategic Roadmap: EPA's Commitments to Action 2021-2024, U. S. Environemental Protection Agency. Washington, DC.

US EPA (2021d). Memorandum Regarding Per- and Polyfluoroalkyl Substances, U. S. Environemental Protection Agency. Washington, DC.

US EPA (2023a). Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water (Public Comment Draft). Washington DC, United States Environmental Protection Agency.

US EPA (2023b). Toxicity Assessment and Proposed Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water (Public Comment Draft). Washington DC, United States Environmental Protection Agency.

US EPA Scientific Advisory Board (2022). Review of EPA’s Analyses to Support EPA's National Primary Drinking Water Rulemaking for PFAS FINAL REPORT, dated August 22, 2022. Access 2022].

Vahter M (1999). Methylation of inorganic arsenic in different mammalian species and population groups. *Sci Prog* 82 (Pt 1): 69-88.

Valvi D, Hojlund K, Coull BA, et al. (2021). Life-course Exposure to Perfluoroalkyl Substances in Relation to Markers of Glucose Homeostasis in Early Adulthood. *J Clin Endocrinol Metab* 106(8): 2495-2504.

van Esterik J, Sales LB, Dollé M, et al. (2016). Programming of metabolic effects in C57BL/6JxFVB mice by in utero and lactational exposure to perfluorooctanoic acid. *Archives of toxicology* 90(3): 701-715.

Vanden Heuvel JP, Thompson JT, Frame SR, Gillies PJ (2006). Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: a comparison of human, mouse, and rat peroxisome proliferator-activated receptor-α,-β, and-γ, liver X receptor-β, and retinoid X receptor-α. *Toxicological Sciences* 92(2): 476-489.

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

Wan HT, Wong AY-M, Feng S, Wong CK-C (2020). Effects of in utero exposure to perfluorooctane sulfonate on placental functions. *Environmental science & technology* 54(24): 16050-16061.

Wang J, Yan S, Zhang W, Zhang H, Dai J (2015). Integrated proteomic and miRNA transcriptional analysis reveals the hepatotoxicity mechanism of PFNA exposure in mice. *Journal of proteome research* 14(1): 330-341.

Wang J, Zhang J, Fan Y, et al. (2022). Association between per- and polyfluoroalkyl substances and risk of gestational diabetes mellitus. *Int J Hyg Environ Health* 240: 113904.

Wang Z, Shi R, Ding G, et al. (2022). Association between maternal serum concentration of perfluoroalkyl substances (PFASs) at delivery and acute infectious diseases in infancy. *Chemosphere* 289: 133235.

Wang Z, Wang J, Zhu Y, et al. (2021). Cause-specific mortality among survivors from T1N0M0 renal cell carcinoma: A registry-based cohort study. *Frontiers in oncology* 11.

Wang Z, Zhang T, Wu J, et al. (2021). Male reproductive toxicity of perfluorooctanoate (PFOA): Rodent studies. *Chemosphere* 270: 128608.

Wasserstein RL, Lazar NA (2016). The ASA statement on p-values: context, process, and purpose. Am Statistician 70(2): 129-133.

Weiss JM, Jones B, Koekkoek J, Bignert A, Lamoree MH (2021). Per-and polyfluoroalkyl substances (PFASs) in Swedish household dust and exposure of pet cats. *Environmental Science and Pollution Research* 28(29): 39001-39013.

White SS, Calafat AM, Kuklenyik Z, et al. (2007). Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. *Toxicological Sciences* 96(1): 133-144.

White SS, Stanko JP, Kato K, et al. (2011). Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. *Environmental health perspectives* 119(8): 1070-1076.

Wielsoe M, Kern P, Bonefeld-Jorgensen EC (2017). Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. *Environ Health* 16(1): 56.

Williams RR, Horm JW (1977). Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* 58(3): 525-547.

Winquist A, Steenland K (2014). Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. *Environ Health Perspect* 122(12): 1299-1305.

Wolf CJ, Schmid JE, Lau C, Abbott BD (2012). Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARα) by perfluoroalkyl acids (PFAAs): Further investigation of C4–C12 compounds. *Reproductive toxicology* 33(4): 546-551.

Wolf CJ, Takacs ML, Schmid JE, Lau C, Abbott BD (2008). Activation of mouse and human peroxisome proliferator− activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. *Toxicological Sciences* 106(1): 162-171.

Wong F, MacLeod M, Mueller JF, Cousins IT (2014). Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: evidence from population-based pharmacokinetic modeling. *Environmental science & technology* 48(15): 8807-8814.

Woskie SR, Gore R, Steenland K (2012). Retrospective exposure assessment of perfluorooctanoic acid serum concentrations at a fluoropolymer manufacturing plant. *Annals of occupational hygiene* 56(9): 1025-1037.

Xie Y, Yang Q, Nelson BD, DePierre JW (2003). The relationship between liver peroxisome proliferation and adipose tissue atrophy induced by peroxisome proliferator exposure and withdrawal in mice. *Biochemical pharmacology* 66(5): 749-756.

Xu H, Zhou Q, Zhang J, et al. (2020). Exposure to elevated per- and polyfluoroalkyl substances in early pregnancy is related to increased risk of gestational diabetes mellitus: A nested case-control study in Shanghai, China. *Environ Int* 143: 105952.

Yamada T, Cohen SM, Lake BG (2021). Critical evaluation of the human relevance of the mode of action for rodent liver tumor formation by activators of the constitutive androstane receptor (CAR). *Critical reviews in toxicology* 51(5): 373-394.

Yan S, Wang J, Zhang W, Dai J (2014). Circulating microRNA profiles altered in mice after 28 d exposure to perfluorooctanoic acid. *Toxicology letters* 224(1): 24-31.

Yang J, Wang H, Du H, et al. (2021). Serum perfluoroalkyl substances in relation to lipid metabolism in Chinese pregnant women. *Chemosphere* 273: 128566.

Yang Q, Ito S and Gonzalez FJ (2007). Hepatocyte-restricted constitutive activation of PPAR alpha induces hepatoproliferation but not hepatocarcinogenesis. *Carcinogenesis* 28(6): 1171-1177.

Ye WL, Chen ZX, Xie YQ, et al. (2021). Associations between serum isomers of perfluoroalkyl acids and metabolic syndrome in adults: Isomers of C8 Health Project in China. *Environ Res* 196: 110430.

Yin W, Carballo-Jane E, McLaren DG, et al. (2012). Plasma lipid profiling across species for the identification of optimal animal models of human dyslipidemia [S]. *Journal of lipid research* 53(1): 51-65.

Yu G, Jin M, Huang Y, et al. (2021). Environmental exposure to perfluoroalkyl substances in early pregnancy, maternal glucose homeostasis and the risk of gestational diabetes: A prospective cohort study. *Environ Int* 156: 106621.

Yu S, Feng WR, Liang ZM, et al. (2021). Perfluorooctane sulfonate alternatives and metabolic syndrome in adults: New evidence from the Isomers of C8 Health Project in China. *Environ Pollut* 283: 117078.

Yuan JM, Castelao JE, Gago-Dominguez M, Ross RK, Yu MC (1998). Hypertension, obesity and their medications in relation to renal cell carcinoma. *Br J Cancer* 77(9): 1508-1513.

Zahm S, Bonde JP, Chiu WA, et al. (2023). Carcinogenicity of perfluorooctanoic acid and perfluorooctanesulfonic acid. *The Lancet Oncology* 25(1): 16-17.

Zare Jeddi M, Dalla Zuanna T, Barbieri G, et al. (2021). Associations of Perfluoroalkyl Substances with Prevalence of Metabolic Syndrome in Highly Exposed Young Adult Community Residents-A Cross-Sectional Study in Veneto Region, Italy. *Int J Environ Res Public Health* 18(3).

Zare Jeddi M, Soltanmohammadi R, Barbieri G, et al. (2021). To which extent are per- and poly-fluorinated substances associated to metabolic syndrome? *Rev Environ Health*.

Zeeshan M, Zhang YT, Yu S, et al. (2021). Exposure to isomers of per- and polyfluoroalkyl substances increases the risk of diabetes and impairs glucose-homeostasis in Chinese adults: Isomers of C8 health project. *Chemosphere* 278: 130486.

Zeng XW, Qian Z, Emo B, et al. (2015). Association of polyfluoroalkyl chemical exposure with serum lipids in children. *Sci Total Environ* 512-513: 364-370.

Zhang Y, Beesoon S, Zhu L and Martin JW (2013b). Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. *Environ Sci Technol* 47(18): 10619-10627.

Zhang H, Shi Z, Liu Y, Wei Y, Dai J (2008). Lipid homeostasis and oxidative stress in the liver of male rats exposed to perfluorododecanoic acid. *Toxicology and Applied Pharmacology* 227(1): 16-25.

Zhang YT, Zeeshan M, Su F, et al. (2022). Associations between both legacy and alternative per- and polyfluoroalkyl substances and glucose-homeostasis: The Isomers of C8 health project in China. *Environ Int* 158: 106913.

Zheng F, Sheng N, Zhang H, et al. (2017). Perfluorooctanoic acid exposure disturbs glucose metabolism in mouse liver. *Toxicology and Applied Pharmacology* 335: 41-48.