APPENDIX D

RESPONSES TO COMMENTS ON DWQI HEALTH EFFECTS SUBCOMMITTEE REPORT: "PUBLIC REVIEW DRAFT - HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT: PERFLUOROOCTANOIC ACID (PFOA)"

February 13, 2017

Please note:

- ***As the Drinking Water Quality Institute (DWQI) serves as an advisory body which makes recommendations to the NJ Department of Environmental Protection, and DWQI's recommendation is not a rulemaking that is subject to the requirements of the Administrative Procedure Act, a formal response to public comments received on draft subcommittee documents is not required. However, the subcommittee would like to address public comments in detail in order to provide clarification with respect to its draft document and to address any changes made to the document based on those comments when appropriate.***

- ***Although some comments are summarized for brevity, it is the Health Effects Subcommittee's intent to address all points made in the comments in this document.***

- ***Page numbers mentioned in the responses refer to the numbered pages in the draft health-based maximum contaminant level support document: perfluorooctanoic acid (pfoa) linked here.***

Ten submissions with comments relevant to the draft Health-based MCL Support Document were received. Links to the comments are provided below.

- Alan Ducatman, MD, MS, Professor of Public Health and Professor of Medicine at West Virginia University, submitted a letter (Comment 1).
- Philippe Grandjean, physician and environmental epidemiologist, and Adjunct Professor of Environmental Health of the Harvard T.H. Chan School of Public Health, submitted a letter (Comment 2).
- Delaware Riverkeeper Network sent a technical analysis report prepared by Cambridge Environmental Consulting (Comment 3 – Health Effects).
- Department of the Air Force submitted a letter (Comment 4).
- U.S. Environmental Protection Agency sent comments regarding specifically "Appendix 2 – Comparison of USEPA Office of Water Health Advisory and DWQI Recommended Health-Based MCL for PFOA" (Comment 5).
- Green Science Policy Institute submitted a letter (Comment 6).
- Environment New Jersey sent comments regarding the information on PFOA that was presented at the September 22 meeting of the DWQI (Comment 7).

- Environmental Working Group submitted a letter (Comment 8).
- Chemistry Council of New Jersey sent a letter outlining general comments and comments specific to the Health Effects Subcommittee. Earlier comments submitted in June 2014 in response to the 2014 DWQI request for technical information were attached (Comment 9 – 1; Comment 9 – 2).
- Silent Spring Institute submitted a letter (Comment 10).

Comments from Environment New Jersey and Alan Ducatman support the draft Health-based MCL. Comments from Delaware Riverkeeper Network and the technical report submitted on their behalf, Environmental Working Group, Green Science Policy Institute, Philippe Grandjean, and Silent Spring Institute state that the draft Health-based MCL is not stringent enough to protect human health. Comments from the Chemistry Council of New Jersey generally state that the draft Health-based MCL is too stringent, and the Department of the Air Force suggests the USEPA Health Advisory level is sufficiently protective of human health effects. USEPA comments only on the DWQI review of the USEPA Health Advisory for PFOA, and it does not comment on the Health-based MCL developed by the Health Effects Subcommittee.

All comments relevant to the draft Health-based MCL Support Document were considered by the Health Effects Subcommittee. All Subcommittee members participated in reviewing and responding to the comments, and in the decisions about revisions to the draft Health Effects Support Document that were made based on the comments.

The final Health-based MCL Support Document includes a few additional citations suggested by the commenters and some minor edits to clarify the intended meaning in a few places. There are no substantive revisions or changes in the conclusions from the draft document.

GENERAL COMMENTS

1. General support for Health Effects Subcommittee evaluation

COMMENTS: *"The health effects report document provides a thorough and detailed summary on the state of the science regarding human health effects from PFOA exposure. In particular, Appendix 2 and the critique of the EPA Health Advisory value for PFOA highlight significant concerns with the EPA set level of 70 ng PFOA per liter of water."* (Environmental Working Group)

"We would like to complement the Subcommittee Members on the excellent work that went into reviewing, evaluating, and summarizing the existing toxicological and epidemiological evidence associated with exposure to PFOA." (Green Science Policy Institute)

"The NJ--proposed health based maximum of 14 ppt represents excellent science, and thorough risk assessment; it is scientifically defensible and practically achievable

...The document considers pregnant women and future generations (developing humans) as susceptible populations…

… The document is cognizant that important human studies show consistent associations several important biomarker outcomes, including but not limited to alterations of total and LDL cholesterol, and markers of immune response…

… In addition, a number of toxicology studies, reviewed by the NJ scientists, do suggest reproductive and developmental risks that have not yet been adequately studied in humans…

… The document also performs the needed task of listing the areas of scientific uncertainty. That is important as it openly assists readers of all perspectives.… In summary, a thorough review of the available science has provided a protective yet realistic target. The proposed standard is science-based, achievable, and in the public interest." (Alan Ducatman)

RESPONSE: These supportive comments are acknowledged.

2. Consideration of additional references

COMMENT: *The DWQI recommendation is too stringent based on objective analysis of available science and data. The DWQI should review the detailed scientific data and literature that it either ignored or missed before making a recommendation on PFOA.* (Chemistry Council of NJ)

RESPONSE: The DWQI, including the Health Effects Subcommittee, has thoroughly and objectively evaluated the relevant scientific information on PFOA. The Health Effects Subcommittee conducted a literature review and a detailed evaluation of PFOA during 2009-2010, although a Health-based MCL recommendation was not finalized at that time. An extensive and highly cited review of PFOA as an emerging drinking water contaminant was subsequently published in a peer-reviewed journal by several current and former Subcommittee members in 2012 (Post et al., 2012). As discussed in Appendix 1 of the draft Health-based MCL Support Document, the Health Effects Subcommittee conducted an initial literature search in April 2015 that yielded more than 2000 citations. This initial literature search was updated with additional monthly literature searches. In May 2014, the DWQI posted a request for submission of additional technical information, and the information received in response to the request was considered by the Health Effects Subcommittee.

COMMENT: *"…we urge DWQI to review more scientific data and literature … enHealth, Government of Canada, Health Council of the Netherlands, Chang et al., 2014*" (Chemistry Council of NJ)

RESPONSE: The Health Effects Subcommittee is familiar with these documents, as well as reviews by other international agencies, and has reviewed them in depth. A summary of relevant information on each of these documents is presented below:

- **enHealth Statement: Interim national guidance on human health reference values for per- and poly-fluoroalkyl substances for use in site investigations in Australia. (2016; Environmental Health Standing Committee of the Australian Health Protection Principal Committee)**.

The Environmental Health Standing Committee of the Australian Health Protection Principal Committee (enHealth) considered a number of existing risk-based values for PFOA developed by authorities in several nations. They chose to use the European Food Safety Authority (EFSA; 2008) Tolerable Daily Intake (TDI) of 1.5 ug/kg/day as the basis for a Drinking Water Quality Guideline of 5000 ng/L (5 ug/L).

DWQI members have previously evaluated the basis for the EFSA (2008) TDI and concluded that it is not scientifically supportable or health protective. In recognition that the current TDI is not up to date, EFSA is currently reviewing and updating its TDI for PFOA (http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2015-00526). The current EFSA TDI is based on increased liver weight in rodents, and does not consider the more sensitive toxicological endpoints that occur at lower doses. EFSA (2008) came to similar conclusions as the HE Subcommittee about the validity of increased rodent liver weight as the basis for risk assessment of PFOA. Importantly, the TDI is based on administered dose, and it includes only an additional uncertainty factor of 2 to account for the large toxicokinetic differences between humans and rodents. As discussed in detail in the draft Health-based MCL Support Document (e.g. p. 5, 42, 206, 218) it is generally accepted that the comparison between animals and humans should quantitatively consider the much higher internal dose that will result from the same administered dose in humans and animal, either by use of serum PFOA levels or the ratio of half-lives in the two species.

The enHealth Drinking Water Quality Guideline of 5000 ng/L (5 ug/L) is not scientifically supportable and is unquestionably far higher than can be considered to be health-protective. Ongoing exposure to this drinking water level would result in serum PFOA levels of over 500 ng/ml, on average, far higher than the range associated with multiple health effects.

- **Government of Canada. June 2016. Perfluorooctanoic Acid (PFOA) in Drinking Water, Document for Public Consultation.**

In this document, a Maximum Allowable Concentration (MAC) for PFOA in drinking water of 200 ng/L (0.2 µg/L) is proposed for public comment. It is based on increased liver weight and hepatocellular hypertrophy. The authors of the document came to similar conclusions as the Health Effects Subcommittee about the validity of increased rodent liver weight as the basis for risk assessment of PFOA. A value of 30,000 ng/L (30 µg/L) intended to be protective for carcinogenic effects was also developed, but it was not used as the basis for the MAC because the non-cancer value was more stringent.

During the public comment period for the Health Canada document, Dr. Keith Cooper, Health Effects Subcommittee member and DWQI Chair, submitted detailed comments about the reasons that the proposed MAC of 200 ng/L is not sufficiently health protective.

The major points in the comments were:

- The increases in serum PFOA levels in infants and older individuals that will result from exposure to 200 ng/L in drinking water were not considered. These serum levels exceed the serum levels that are consistently associated with multiple human health effects.

- Sensitive toxicological endpoints were not considered in developing the proposed MAC.

- The proposed Health-based Value of 30,000 ng/L for carcinogenic effects is not sufficiently protective. It does not consider mode of action data from animal studies or exposure levels associated with increased cancer risk in humans.

- **Health Council of the Netherlands. 2013. Perfluorooctanoic acid and its salts – Evaluation of the carcinogenicity and genotoxicity.**

A summary of the following information regarding Health Council of the Netherlands (2013) has been added to the cancer epidemiology section that starts on p. 83 of the draft Health-based MCL Support Document:

Health Council of the Netherlands (2013) evaluated the carcinogenic properties of PFOA, and it does not develop a quantitative risk assessment for PFOA. It concludes

that the available data are insufficient to evaluate its carcinogenic properties. However, the document notes that: *"The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of perfluorooctanoic acid and its salts, no IARC monographs are available."*

The Health Council of the Netherlands thus did not consider the more recent IARC (2016) conclusion that PFOA is possibly carcinogenic to humans. Additionally, the criteria used by the Health Council of the Netherlands to determine the carcinogenicity classification are different from those used by USEPA, NJDEP, and the DWQI. https://www.gezondheidsraad.nl/sites/default/files/A1007_0.pdf.

- **Chang ET, Adami HO, Boffetta P, Cole P, Starr TB, and Mandel JS. 2014. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and cancer risk in humans. Crit Rev Toxicol. 44(S1):1-81.**

A citation to Chang et al. (2014) and a summary of the information below has been added to the cancer epidemiology section that starts on p. 83 of the draft Health-based MCL Support Document:

This review article primarily focuses on human epidemiological data, with a short section on carcinogenicity in rodent studies. It does not develop a quantitative risk assessment for PFOA. The authors conclude that the "*existing epidemiological evidence does not support the hypothesis of a causal association between PFOA or PFOS exposure and cancer in humans. However, further research on this topic is warranted.*" The Health Effects Subcommittee notes that the draft Health-based MCL is not based on a conclusion that there is causal link between PFOA exposure and cancer in humans. As above, Chang et al. (2014) conclude that causality for PPOA and human cancer is not a settled issue. They suggest that quantitative exposure assessment at industrial facilities in Asia that continue to produce or use PFOA and/or PFOS (now phased out in the U.S.) could be used as the basis for future cohort studies with sufficient follow up time. Additionally, continued follow-up of existing cohorts with use of cancer incidence data from cancer registries could provide further information about human cancer risk of PFOA and PFOS.

3. Presentation of scientific evidence and uncertainties related to PFOA's health effects.

COMMENT*: "**The document also performs the needed task of listing the areas of scientific uncertainty. That is important as it openly assists readers of all perspectives."* (Alan Ducatman)

RESPONSE: This comment is acknowledged.

COMMENT: "*Unlike DWQI, USEPA and other jurisdictions recognize the lack of scientific evidence and uncertainties associated with the science related to any health effects associated with PFOA."* **(**Chemistry Council of NJ)

RESPONSE: Like all of the other government agencies that have developed drinking water values for PFOA, DWQI recognizes that uncertainties are associated with the risk assessment. This is also the case for risk assessments of other environmental contaminants. As indicated by the number of studies that were located in the literature search and reviewed in the draft Health-based MCL Support Document, more information is available on human and animal health effects of PFOA than for most other drinking water contaminants evaluated by the DWQI.

COMMENT: "*Overall, we find the support document to be extremely biased in its characterization of PFOA risks. DWQI did not appropriately handle the uncertainty and inconsistency within the database for health effects associated with PFOA exposure – regarding both the animal toxicity study data and human epidemiology data. DWQI appears to have used data selectively to support its analysis, rather than considering the full weight of evidence. Studies and findings that support DWQI's conclusions were presented with high confidence and little mention of weaknesses or limitations, while studies and findings that demonstrate inconsistent and/or conflicting interpretations were either not provided or were presented in a manner that over emphasized weaknesses and limitations in those studies."* (Chemistry Council of NJ)

RESPONSE: The Health Effects Subcommittee does not agree that the draft Health-based MCL Support Document presents a biased discussion of the human and animal health effects data for PFOA. Detailed individual study tables and summary tables present the relevant information for studies of both human and animal endpoints that were reviewed in depth. For each human health endpoint, the complete epidemiologic database was evaluated regardless of positive or negative findings, study details were presented in an equivalent manner for each relevant study, and a conclusion was made about the level of evidence for an association. For the toxicological endpoints that were used as the quantitative basis for the risk assessment, information on all relevant studies is presented in detailed individual study

tables. For all toxicological endpoints that were reviewed in depth (including endpoints not used as the basis for quantitative risk assessment), key information on all relevant studies is presented in summary tables that compare the design and results of the studies, and the information on each of the endpoints is synthesized in the text. When results of a single study differ from results of all of the other studies of the same endpoint, the reasons that might account for differing results were evaluated and are discussed in the document.

4. DWQI classification of PFOA as a developmental toxicant is not supported by available evidence and contributes to "unsupported" public concern of increased risk to women of childbearing age and infants.

COMMENTS: "*Despite evidence to the contrary, DWQI classifies PFOA as a developmental toxicant, which not only adds an unwarranted uncertainty factor, but also contributes to the public's unsupported concern for increased risk for women of childbearing age and infants."* (Chemistry Council of NJ)

"Not only does consideration of possible PFOA-mediated developmental effects result in a lower MCL recommendation by the unwarranted extra uncertainty factor, the classification of PFOA as a developmental toxicant contributes to the public's unsupported concern for increased risk for women of childbearing age and infants." (Chemistry Council of NJ)

RESPONSE: This comment is factually incorrect. It is well established that PFOA is a developmental toxicant that causes multiple developmental types of developmental toxicity in animals (e.g. full litter resorptions, decreased postnatal survival and growth, delayed development, and accelerated sexual maturation in males). Additionally, as reviewed in the draft Health-based MCL Support Document (p. 79-81), two recent systematic reviews of effects of PFOA on fetal growth in humans quantified the decrease in birth weight per unit increase in serum PFOA. One of these reviews determined the descriptor for strength of evidence and concluded that there is "sufficient" human evidence, the strongest descriptor, that developmental exposure to PFOA reduces fetal growth in humans.

It should be noted that the recent USEPA Drinking Water Health Advisory for PFOA (USEPA, 2016a), which is mentioned by the same commenter (below), is based on developmental effects. USEPA (2016a) states that "PFOA is known to be transmitted to the fetus in cord blood and to the newborn in breast milk" and that "the developing fetus and newborn are particularly sensitive to PFOA-induced toxicity," and that "due to the potential increased susceptibility during the time period of pregnancy and lactation, USEPA used drinking water intake and body weight parameters for lactating women in the calculation of a lifetime HA for this target population during this potential critical time period."

5. USEPA has already developed a Health Advisory for PFOA that is higher than DWQI Health-based MCL

COMMENT: *"The federal United States Environmental Protection Agency (USEPA) and other agencies that have comprehensively reviewed the available scientific evidence recognize the uncertainty in the available data and do not share DWQI's perspective on potential health effects of PFOA in drinking water at the proposed MCL."* (Chemistry Council of NJ)

COMMENT: *"The DWQI's draft recommendation for an MCL of 14 ppt for PFOA significantly exceeds EPA's health advisory, and fails to adequately explain why EPA's conclusions are defective. DoD is concerned that setting an MCL at such a drastically lower level could result in significant costs, while failing to provide any measurable health benefit beyond that already provided by the 70 ppt limit that EPA deemed safe only six days ago in their clarification memo."* (Department of the Air Force)

RESPONSE: The Health Effects Subcommittee is aware of the USEPA PFOA Health Advisory. The Health-based MCL Support Document includes a detailed review of the USEPA advisory in Appendix 2. The Health Effects Subcommittee concludes that the USEPA Health Advisory is not sufficiently protective of human health. The reasons for this conclusion are provided in Appendix 2.

USEPA submitted comments regarding the Health Effects Subcommittee review of the USEPA PFOA Health Advisory. A response to the USEPA comments is presented below.

MARGIN OF EXPOSURE

COMMENT: *"DWQI should explain what margin of exposure (MOE) is afforded by the total set of uncertainty factors it uses to derive the MCL."*

"For example only, some jurisdictions include a scientific alternative that allows for an MOE or "margin of safety" approach… which melds the animal data with human biomonitoring data. DWQI should clearly explain why the MOE findings for PFOA set forth in the Health Canada (2012) document and, specifically, the "margin of safety" found by Canadian authorities are (or are not) appropriate scientific research to consider when protecting health in the state of New Jersey." (Chemistry Council of NJ)

"The Health Canada (2012) "Screening Assessment Report: Perfluorooctanoic Acid, its Salts, and its Precursors" concluded that: "Comparison of the PFOA serum levels associated with adverse effects in laboratory animals … with the serum or plasma levels

found in non-occupationally exposed adults, infants and children … results in margins of exposure greater than 660. These margins are considered to be adequately protective to account for uncertainties in the hazard and exposure databases.

Thus, Health Canada (2012) did not find it necessary to apply additional "uncertainty factors" like DWQI chose to do because the MOE or "margin of safety" in biomonitoring results was sufficient. If DWQI believes that the MOE between PFOA serum levels of NJ citizens and adversely impacted laboratory animals requires the safety factors because of a specific NJ public policy, then DWQI should clearly state their calculated NJ MOE for transparency to the public and regulatory authorities regarding the "margin of safety" being included in the proposed 14 ppt PFOA MCL. CCNJ/SRIN do not believe DWQI has the data to support an MOE analysis; specifically, in the September 22, 2016 meeting materials, DWQI provided the following in a PowerPoint presentation that stated that:"Biomonitoring data specific to New Jersey have not been collected." Therefore, because no biomonitoring data specific to New Jersey have been collected, New Jersey is unable to demonstrate to the public that the State's citizens are any more at risk from PFOA accumulation in serum than people in other jurisdictions, so it is unclear why a more restrictive draft MCL is appropriate for its citizenry." (Chemistry Council of New Jersey)

RESPONSE: The commenter misstates the purpose and conclusions of the Health Canada (2012) risk assessment that they cited. Health Canada (2012) is not relevant to the development of a human health value for PFOA in drinking water. It does not develop a Reference Dose, health-based drinking water criterion, or other health-based value for PFOA, and the MOE approach presented in Health Canada (2012) is not intended for use in development of such health-based values.

The purpose of the assessment presented in Health Canada (2012) was to determine whether PFOA meets one or more of the criteria listed in Section 64 of the Canadian Environmental Protection Act (CEPA) 1999. The CEPA 1999 evaluations relate to whether restrictions are needed regarding manufacture, transport, use, storage, and final disposal of products containing the chemical being reviewed, similar to the evaluations conducted by USEPA TSCA, and the criteria listed in Section 64 are used to determine whether a chemical should be listed as harmful according to laws and regulations analogous to USEPA TSCA.

One of the criteria for a substance to be considered harmful under CEPA 1999 is if it "is entering or could enter the environment in quantities or concentrations or under conditions that constitutes or may constitute a danger to human life or health in Canada" (https://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=52CD77FA-1). The MOE assessment was used to evaluate whether PFOA meets this criterion. It compared upper bound serum levels in the general population with serum levels that are associated with

adverse effects in laboratory animals. The purpose of the Health Canada (2012) MOE assessment is similar to the purpose of the draft 2005 PFOA risk assessment developed by the USEPA Office of Pollution Prevention and Toxics (OPPT), which is responsible for implementation of TSCA. Like Health Canada, OPPT evaluated MOEs between serum levels in the general population and serum levels where toxicity occurs in animals.

In contrast, Health Canada (2016), which is also cited elsewhere in the comments from the same commenter, develops a Maximum Acceptable Concentration (MAC) for PFOA in drinking water. The MAC developed by Health Canada (2016) is based on the application of uncertainty factors, comparable to the approach used by the DWQI to develop a Health-based MCL.

SIGNIFICANCE OF INCREASES IN HUMAN SERUM PFOA LEVELS PREDICTED FROM DRINKING WATER EXPOSURES

COMMENT: *"DWQI compares predicted serum PFOA levels to background levels but fails to provide any context regarding the proposed Target Human Serum level."* (Chemistry Council of NJ)

"DWQI conflates two related but very distinct concepts – serum concentrations that exceed background, and serum concentrations that are within a range that may present a health risk. It is inappropriate to present the increase in PFOA serum levels over background serum levels for exposures at select PFOA drinking water concentrations (see Figures E-1, 1 and 8 and associated test) without discussing the uncertainty and variability in the underlying assumptions and without tying serum levels to actual risk. DWQI's proposed MCL is based on their calculated Target Human Serum level of 14.5 ng/mL, but DWQI does not discuss … the fact that serum levels that exceed NHANES background serum levels but are below the Target Human Serum level would be interpreted as presenting a de minimis risk. DWQI should address these points so the public is not misled by DWQI's presentation of NHANES baseline levels." (Chemistry Council of NJ)

RESPONSE: The section of the draft Health Effects Support Document entitled *Relationship between drinking water and serum concentrations in exposed communities* clearly discusses that there is inter-individual variability in blood PFOA serum levels from a given drinking water concentration and discusses the sources of this variability. The document states that the information presented in the bar graphs and in Table 5 are average predictions of serum level increase, and that there is individual variability in the serum level increase from a certain drinking water concentration. An additional mention of this has been added to the final document to ensure that this is clear to the reader.

As stated in several places in the draft Health-based MCL Support Document (e.g. p. 87, 203, 220), as well as in the comment from A. Ducatman in the Human Epidemiology section (below), serum PFOA levels prevalent in the general population (e.g. 5 ng/ml or below) are associated with several human health effects, with multiple criteria supporting causality for some endpoints. The draft Health-based MCL Support Document (p. 209) also discusses that the most sensitive developmental effects seen in toxicological studies support a Target Human Serum Level of 0.8 ng/ml, well below the general population median value, 2.1 ng/ml. Therefore, data from both human and animal studies suggest a need for caution about drinking water exposures that increase serum PFOA levels.

COMMENT: "*DWQI presented the increase in serum levels over background for exposures at a range of PFOA drinking water concentrations. This discussion does not contribute any meaningful information to the potential health risks related to PFOA exposure and should not be provided (numerous times) in the health-based MCL support document for the following reasons:*

This analysis relies exclusively on the assumptions within Lorber et al. (2011) and DWQI's analysis does not demonstrate or even mention the variability and uncertainty in this analysis. For example, DWQI's Table 4 presents a range of serum/plasma half-lives, however, the assumptions within Lorber et al. (2011) rely on only one single PFOA half-life estimate. More explanation is needed regarding the basis for the range. (Chemistry Council of NJ)

RESPONSE: The human half-life values in Table 4 (p. 45) of the draft Health-based MCL Support Document come from studies of different populations (e.g. adults after exposure to contaminated drinking water ended; average of children and adults after drinking water exposure ended; retired workers; highly exposed and less exposed adults and children during the initial and longer term periods after drinking water exposure ended.) The half-life of 2.3 years from adults after drinking water exposure ended is the shortest human half-life reported for PFOA in the literature. Use of any of the other half-life values would result in prediction of higher serum PFOA levels from a given drinking water exposure than those shown in the table and graphs in the document.

COMMENT: *DWQI's focus on exceedance of background levels is at odds with USEPA's definition of toxicity reference values used to derive criteria protective of adverse health effects. USEPA (2002) recommends the following definition for a noncancer threshold value, "an estimate of an exposure, designated by duration and route, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime." Accordingly, for the MCL for PFOA that is calculated from a Target Human Serum level, there is high confidence that serum concentrations below this*

level present a de minimis risk, even if such concentrations are elevated above NHANES baseline levels. Furthermore, without additional evaluation of dose-response relationships for PFOA using serum data, no specific health risk statements can be made regarding human serum levels that exceed the Target Human Serum level.

Nowhere does DWQI discuss the interval between NHANES background serum levels and their calculated Target Human Serum level of 14.5 ng/mL. This is an egregious risk communication error. Even though an increase in serum PFOA level above baseline does not equate with a health risk to an individual, the public may incorrectly draw this conclusion. We recommend that DWQI remove the calculation of PFOA serum level increases for various drinking water concentrations from the support document entirely. At the very least, this analysis should be relegated to an appendix and not have such a prominent discussion multiple times throughout the main support document, and should include transparent discussion of where target human serum levels for the critical effect fall relative to NHANES. (Chemistry Council of NJ)

RESPONSE: It is discussed in several places in the draft Health-based MCL Support Document (e.g. p. 87, 203, 220), and in the comment from A. Ducatman below, that serum PFOA levels prevalent in the general population, well below the Target Human Serum Level of 14.5 ng/ml, are associated with human health effects, with multiple criteria supporting causality for some endpoints. It is also discussed that the most sensitive developmental effects observed in toxicological studies support a Target Human Serum Level within the general population range.

Relevant to this point, it is noted that the German Human Biomonitoring Commission recently developed a Human Biomonitoring Level I (the serum level below which adverse health effects are not expected) for PFOA of 2 ng/ml, close to the current median PFOA serum level in the U.S. general population. This HBM I is based on the serum PFOA levels associated with increased time to pregnancy, decreased fetal growth, increased serum cholesterol, and decreased immune response in humans, and with delayed mammary gland development in mice (Apel et al., 2016. Int. J. Hygiene and Env. Health, in press).

Therefore, the Health Effects Subcommittee concludes that additional exposure from drinking water, including at the level of the draft Health-based MCL, may potentially pose some risk of health effects. For this reason, it cannot be definitively concluded that lifetime exposure to the drinking water concentrations discussed, including the recommended Health-based MCL, are protective of sensitive subpopulations with a margin of exposure.

DEVELOPMENT OF REFERENCE DOSE

1. Selection of non-cancer endpoints

COMMENT: "*Justification is needed for the selected noncancer endpoints, including transparent and fair representation of the actual adversity of selected endpoints. DWQI presented results from toxicity studies linking PFOA exposure to multiple noncancer endpoints of concern and claimed that they yield relatively consistent points of departure (POD) for calculating a human equivalent dose. However, DWQI did not apply a true weight-of-evidence analysis of the study data, nor a discussion regarding the severity of effects across the range of endpoints."* (Chemistry Council of NJ)

RESPONSE: The non-cancer endpoints selected for quantitative evaluation are thoroughly discussed in the Health-based MCL Support Document (e.g. p. 205-206, p. 210), including why they are appropriate as the basis of the risk assessment according to the risk assessment guidelines followed by USEPA, NJDEP, and the DWQI. The draft Health-based MCL Support document includes detailed tables and discussion in the text that provide the weight of evidence for the toxicological effects selected for detailed review. The information in the detailed tables is presented so that the doses at which effects occurred or did not occur in each study can be easily compared, and the information for each endpoint is synthesized in the text. The severity and significance of the endpoints are discussed, particularly for the two endpoints selected for dose-response modeling (increased liver weight/hepatic toxicity and delayed mammary gland development).

The draft Health-based MCL Support Document did not state that the non-cancer endpoints that were reviewed yielded relatively consistent points of departure. It stated (p. 205) that increased liver weight (which can co-occur and/or progress to more severe hepatic toxicity) and delayed mammary gland development after prenatal or neonatal exposure are the most sensitive toxicological endpoints with data that can be used for dose-response modeling. It stated that delayed mammary gland development is the most sensitive toxicological endpoint with data for dose-response modeling, and that hepatic toxicity (as indicated by increased liver weight) is the next most sensitive effect with data for dose-response modeling. It also stated that persistent hepatic toxicity from developmental exposure is an additional sensitive endpoint that occurs at the same low doses as delayed mammary gland development, but that data that can be used for dose-response modeling are not available for this effect. As above, relevant information about studies of these endpoints is presented in depth in tables and text.

2. Use of increased liver weight as a toxicological endpoint

COMMENT: "*Several regulatory agencies have clearly stated that rodent toxicity studies that demonstrate liver hypertrophy in the absence of cell toxicity or other evidence of potential impairment of liver function are not suitable for quantifying risks to humans (TOXSAC 2002; Hall et al. 2012). We strongly agree, and recommend that DWQI provide a more transparent presentation of the data showing PFOA-mediated effects on the rodent liver,including a discussion on where actual liver toxicity is or is not observed along the dose-response continuum."*

"DWQI derived the health-based MCL on increased liver weights in rodents, even though there is strong evidence that at this low dose, the measured change in the liver is an adaptive response associated with normal liver functioning, and not evidence of an adverse effect. Increased liver weight without histopathological changes indicative of cell damage (at the same dose in the same study) should be considered non-adverse. A report by the European Society of Toxicologic Pathology evaluated adverse versus adaptive changes in the liver and concluded that liver weight increases up to 150% of control values may still be considered non-adverse in the context of chemical safety evaluations (Hall et al., 2012).

Additionally, the EPA 2002 guidance document from the Health Effects Division Toxicology Science Advisory Council (TOXSAC 2002) notes that a statistically significant increase in liver size alone (i.e., in the absence of histopathological evidence) is not a reliable indicator of hepatic toxicity. In conclusion, the existing data do not clearly support the liver as an appropriate target organ following low level PFOA exposures. Finally, using established toxicology guidance, the data suggest that liver weight changes in the rodents from Loveless et al. (2006) are adaptive, non-adverse effects." (Chemistry Council of NJ)

RESPONSE: The draft Health-based MCL Support Document (p. 109-115) addresses the points made in this comment by reviewing in great detail the hepatic toxicity from PFOA that co-occurs with or follows increased liver weight of the document. As stated on p. 109 of the document, "…. numerous studies of PFOA have demonstrated that increased liver weight co-occurs with and/or progresses to more severe hepatic effects including increased serum liver enzymes, hepatocellular necrosis, fatty liver, and/or hyperplastic nodules. Additionally, recent studies show that cellular damage indicative of liver toxicity persists until adulthood following developmental exposure to PFOA." Similarly, Butenhoff et al. (2012) suggested that the observations at one year and two years in a chronic study in rats suggest a progression of lesions "from hepatocellular hypertrophy to fatty degeneration to necrosis followed by regenerative hyperplasia." The draft Health-based MCL Support Document (p. 109-115) includes a detailed review of the data from the numerous studies showing co-occurrence or progression of increased liver weight/hepatocellular hypertrophy to more

severe histopathological changes in the liver and increased liver enzymes and/or bile acids to support the conclusions above.

The Health Effects Subcommittee is aware of the recommendations of TOXSAC (2002) and Hall et al. (2012). Both of these documents discuss that increased liver weight or hepatocellular hypertrophy are adverse when they co-occur with or progress to other types of hepatic toxicity, such as described for PFOA above. It should be noted that the primary focus of Hall et al. (2012) is pre-clinical toxicity studies for drug development. Hall et al. (2012) emphasize that the expected duration of exposure must be considered in determining the adversity of hepatic effects such as increased liver weight and hepatocellular hypertrophy. Such effects may be reversible if the anticipated duration of exposure is short, while progression to more severe hepatic effects may occur from longer exposures to the same dose. These duration of exposure considerations are relevant to safety evaluation of drugs, since they are normally only taken for a limited period of time. However, because the Health-based MCL is intended to protect for lifetime exposure, reversibility of effects when exposure ends is not a relevant consideration.

Numerous other risk assessments of PFOA, including those recommended by the same commenter (Health Canada, 2016; enHealth, 2016) and others, are based on increased liver weight and/or hepatocellular hypertrophy. Health Canada (2016) cites the conclusions of Hall et al. (2012) mentioned in the comment above, but concludes that increased liver weight and hepatocellular hypertrophy in rats should be used as the basis for its PFOA risk assessment. It notes that these effects can progress to more serious hepatic toxicity with continued exposure and reviews the data to support this conclusion.

enHealth (2016), also recommended by the commenter, relies on the Tolerable Daily Intake (TDI) developed by EFSA (2008) which is based on increased liver weight in rodents. EFSA (2008) states that, while hepatocellular hypertrophy and increased liver weight are often classified as adaptive and reversible, these effects are possibly related to "effects such as tumour promotion and/or changes in drug-metabolizing enzyme activities, and that reversibility is of limited importance when assessing compounds with high persistence and long biological half-life" such as PFOA.

Finally, the Health Effects Subcommittee notes that, with the exception of the uncertainty factor of 10 for more sensitive developmental effects (e.g. delayed mammary gland development, persistent liver toxicity from developmental exposures), the DWQI Reference Dose of 2 ng/kg/day based on increased liver weight (20 ng/kg/day ÷ 10 = 2 ng/kg/day) is numerically the same as the RfD of 20 ng/kg/day in the USEPA (2016a) Health Advisory based on other toxicological endpoints (delayed ossification and accelerated male puberty in mice).

3. Use of rodent toxicity data as basis for risk assessment.

COMMENT: "*Stronger justification is needed to support the use of rodent toxicity studies with PFOA to infer comparable dose-response relationship in humans. DWQI relied on rodent data despite the consensus among the scientific community regarding the high uncertainty in extrapolating PFOA health effect levels from rodents to humans. We disagree with DWQI's assessment of the PFOA mode of action, specifically regarding the peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and other nuclear receptors, and with DWQI's overall conclusion that rodent data are appropriate for assessing human risk. DWQI's use of rodent liver data is clearly inconsistent with conclusions reached by ATSDR (2015) and other health and environmental regulatory agencies. It is well known that PFOA mediates many of its cellular effects through PPAR-alpha, constitutive androstane receptor (CAR), and pregnane X receptor (PXR). It is also well known that humans are less responsive to the effects of these nuclear receptor signaling pathways. While it may not be currently possible to completely rule out the contribution of other (non-PPAR-alpha) modes of action for many PFOA-mediated effects (especially effects occurring in organs other than the liver), given that rodents are more responsive than humans to many of these nuclear receptor activations, the quantitative relevance of rodent data is dubious at best.*

Animal-to-human extrapolation uncertainty is common in regulatory toxicology. However, with PFOA, the science is clear that rodent data have severe limitations in terms of human relevance. Rather than ignoring this fact, a more scientifically supportable approach would be for DWQI to assess this uncertainty quantitatively. Specifically, if rodent data are to be used to quantify a human threshold value for PFOA, species-specific differences in toxicokinetics and toxicodynamics should be assessed using available modeling tools. DWQI failed to accurately account for the key species-specific differences in a quantitative manner." (Chemistry Council of NJ)

RESPONSE: The Mode of Action section of the draft Health-based MCL Support Document (p. 177-187, p. 188-190, p. 191-198) includes detailed evaluations of the primary data from numerous relevant studies that support the use of rodent data as the basis for risk assessment of PFOA. While some PPAR-alpha activating chemicals have been shown to cause hepatic toxicity through a PPAR-alpha activation mode of action that may not be relevant to humans, several lines of evidence support the conclusion that hepatic effects of PFOA should be considered to be relevant to humans. The DWQI document notes that the dose-response curves for hepatic toxicity and PPAR-alpha activation from PFOA are similar in non-human primates and rats. Additionally, PFOA causes hepatic toxicity in strains of mice lacking PPAR-alpha (PPAR-alpha null), and liver toxicity in these mice is more severe in some cases than in wild type mice of the same strain. Also, increased liver weight does

not correlate with magnitude of PPAR-alpha activation even in standard strains of rodents. The DWQI document also notes that for effects other than liver toxicity, such as developmental and immune system toxicity, available data do not support the conclusion that humans are less sensitive than rodents to PPAR-alpha mediated effects.

The risk assessment presented in the draft Health-based MCL Support Document (p. 209-209, p. 214) does consider species-specific differences in toxicokinetics and toxicodynamics. The default uncertainty factor of 3 is used for toxicodynamic differences, although considerable human data provide support for the conclusion that PFOA causes effects in humans at internal doses (i.e. serum levels) much more than 3-fold below the LOAEL serum PFOA levels from rodent studies. Toxicokinetic differences are accounted by comparison based on internal dose (either through use of serum PFOA data, rather than administered dose, or interspecies half-life ratio).

The Health Effects Subcommittee is aware that the Agency for Toxic Substances and Disease Registry (ATSDR; 2015) draft assessment of PFOA and other perfluoroalkyl compounds dismissed rodent data as the basis for risk assessment. This is in contrast to use of rodent data as the basis for the risk assessments of numerous other agencies, including Health Canada (2016) and enHealth (2016) recommended by this commenter. As a draft, the conclusions of ATSDR (2015) are subject to change based on review of comments that have been submitted to them. The Health Effects Subcommittee notes that NJDEP and NJDOH jointly submitted extensive comments on the ATSDR (2015) draft document that are posted at https://www.regulations.gov/document?D=ATSDR-2015-0004-0003. General conclusion of the NJDEP and NJDOH comments include: "The quality of the draft ATSDR document is inadequate in many instances. The document has not been appropriately updated throughout. Important information is not up to date, and numerous relevant studies (both recent and older) are not cited. In some instances, the presentation of information from studies that are pivotal to ATSDR's major conclusions is inaccurate and/or incomplete," and "ATSDR's decision to dismiss all rodent data for consideration in MRL development does not appear to be scientifically supportable. Furthermore, the presentation of some key studies related to the rationale for this decision is inaccurate and/or incomplete." A detailed discussion of why the decision to dismiss rodent studies for PFOA is not supportable is provided on pages 11 through 13 of the NJDEP/NJDOH comments on the ATSDR draft assessment.

4. Consideration of mammary gland development effects

COMMENTS: *"For some chemicals, the breast is more sensitive than other tissues to low-dose exposures…Rats and mice are useful surrogates for human breast development, because the stages of mammary gland development are similar. Consider lowering standard to be protective of the effects of PFOA on mammary gland development by incorporating*

*mammary gland developmental effects for risk assessment…Research by Rudel et al., 2011; Macon and Fenton, 2013 has shown environmental exposures can alter mammary gland development, disrupt lactation, and increase susceptibility." (*Silent Spring Institute)

"… the proposed drinking water MCL of 14 ng/L for PFOA based on increased relative liver weight is not adequately protective of all population segments…. the standard may be developed based on … evidence of developmental effects shown in rodent studies…these approaches provide more sensitive endpoints with quantitative data to develop an MCL, providing greater protection… an approximate MCL of 1.0 ng/L based on the BMDL determined in the delayed mammary gland developmental effects in mice studies." (Delaware Riverkeeper Network)

"Delayed mammary gland development in mice resulting from developmental exposures to PFOA is a sensitive endpoint. This toxicity effect has been shown in nine different studies (NJDWQI report 2016) …NJDWQI acknowledged these studies, which may result in increased susceptibility to cancer later in life. The NJDWQI states that "The Health Effects Subcommittee chose not to use this (delayed mammary gland development) RfD as the basis for a recommended Health-based MCL, not because of uncertainty about the scientific validity of doing so, but rather because of lack of precedent for use of this endpoint as the primary basis for health-based criteria for environmental contaminants. Instead the Subcommittee arbitrarily applied an additional 10 UF to an unrelated endpoint (increased liver weight that forms the basis for their MCL derivation) to compensate for the more sensitive endpoint (delayed mammary gland development). This is confusing. Why not use the more sensitive endpoint for which adequate toxicity data already exists, including a BMDL, even if that endpoint has not previously been used, versus adding an additional uncertainty factor to an alternate endpoint to compensate for an uncertainty that is, in fact, known?" (Delaware Riverkeeper Network)

"In setting a health-based maximum contaminant level the DWQI identified, but did not utilize, numerous studies completed on animals and humans that show health effects occurring from PFOA exposure at even lower concentration than the studies used. Incorporation of these studies will result in a lowering of the proposed drinking water value for PFOA, potentially to zero. ….. It is imperative that a health-based MCL be truly protective from the known health effects of PFOA exposure. The level of 14 ng PFOA/L water proposed by the DWQI … still falls short of fully protecting public health from the harmful effects of PFOA exposure. EWG recommends that the proposal be updated to incorporate the evidence of PFOA exposure-related effects on mammary gland development …. In our comments we are not providing additional references to studies detailing the impact of PFOA exposure but highlighting the statements made by the DQWI and the lack of incorporating these findings in the final MCL value. With respect to PFOA impact on

mammary gland development the DWQI went through the exercise of calculating an exposure level of 1 ng/L in water to represent the value at which adverse health effects would not be expected. EWG disagrees with the statement that the lack of precedent disqualifies the use of these studies in establishing a MCL for PFOA. As stated by the DWQI: "A Health Based MCL based on this RfD would be 1 ng/L or less. The Health Effects Subcommittee chose not to use this RfD as the basis for a recommended Health-based MCL, not because of uncertainty about the scientific validity of doing so, but rather because of lack of precedent for use of this endpoint as the primary basis for health-based criteria for environmental contaminants. (Environmental Working Group)

"*While it may be argued that this* [human] *evidence may not appropriately represent the toxicity risks associated with PFOA exposures, I note that the DWQI Report also reviewed the studies on PFOA-induced delayed mammary gland development, where the RfD has been calculated to be 0.8 ng/mL serum…the proposed water limit of 14 ng/L would also be too high to provide the desired protection of the exposed population"* (Phillipe Grandjean).

RESPONSE: The Health Effects Subcommittee has considered the issues discussed in these comments, and the draft Health-based MCL Support Document (p. 125-128) reviews the publications about effects of environmental contaminants on the mammary gland that are cited in the comment from the Silent Spring Institute. However, the Health Effects Subcommittee decided not to use this endpoint as the primary basis for the quantitative risk assessment, in large part because there is no precedent for doing so. The Health Effects Subcommittee also notes that the permanent histopathological changes in adulthood observed in mammary glands of developmentally exposed offspring were looked for in only one study. Additionally, only limited data are available regarding the effects of developmental exposure to PFOA on lactational function. Only a single study assessed this endpoint in mice, and this study did not observe a decrease in body weight of offspring nursed by dams with earlier developmental exposure. However, three human studies from different locations found associations of maternal PFOA exposure with decreased duration of breast-feeding, suggesting a potential effect of PFOA on human mammary gland function (Fei et al., 2010; Romano et al., 2015; Timmermann et al., 2016). **If additional future studies continue to support these findings, then this endpoint could be reconsidered for use as the basis for quantitative risk assessment.**

According to current USEPA risk assessment guidance, an uncertainty factor should be applied "if there is concern that future studies may identify a more sensitive effect, target organ, population, or lifestage." See: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1037tr.pdf. Based on consideration of the information summarized above, the Health Effects Subcommittee concludes that it is most appropriate to account for effects on mammary gland development

and other low-dose developmental effects (e.g. persistent liver toxicity from developmental exposures) through incorporation of the default uncertainty factor of 10 into the Reference Dose which has a primary basis of increased liver weight. It should be noted that these low-dose developmental effects occur at much lower doses than the developmental effects used as the basis for the USEPA Health Advisory (delayed ossification and accelerated male puberty).

COMMENTS: "*There is a wide range of findings for this endpoint. DWQI should consider and better present inconsistencies in the database regarding developing mammary gland effects, including negative studies, studies that showed inhibition of mammary gland development, and the studies that showed a stimulation of glandular development. A more thorough analysis is needed regarding the biological significance of the effects, including the relevance of the lack of concurrent adverse effects on reproduction and nursing capabilities for studies for which inhibition of mammary gland development is noted (Macon et al. 2011) (see comment 5 below).*" (Chemistry Council of NJ)

"As DWQI acknowledged, this is a highly uncertain endpoint, with limited support in the rodent toxicology literature and no clear link to human adverse effects. DWQI failed to properly discuss the inconsistency present in the various studies addressing this endpoint and failed to disclose the fact that there was no effect on puberty, reproduction, or nursing capabilities of the mice with delayed mammary gland development (Macon et al. 2011), further indicating that the endpoint is highly uncertain and is not biologically significant or adverse." (Chemistry Council of NJ)

"…basing a regulatory action on this endpoint in a highly variable species (mice) is, as DWQI acknowledged, not done by other jurisdictions. In part, this may be because details that suggest that the murine mammary gland delayed development is not of biological significance in humans (e.g. the White et al. 2011 data had demonstrated that no significant dose-related differences were found in the ability of the CD-1 mice given 1 mg/kg/day to provide nourishment to their young as reflected in measurements of body weight in F1 and F2 pups across a 63-day postnatal period, as the USEPA (2016) document pointed out). This could mean that the gland developmental delay is inconsequential, or biologically insignificant." (Chemistry Council of NJ)

RESPONSE: All of the studies of delayed mammary gland development (including both studies of exposure to pregnant dams, fetuses and neonates, and studies of peripubertal females) are presented and discussed in great detail in the draft Health-based MCL Support Document (p. 128-135, Tables 14A and 14 B on p. 171-176; Appendix 5B), including individual study tables and summary tables that compare protocols and results of the studies. As discussed in the document, delayed mammary gland development from prenatal/early life

exposure was observed in nine separate studies reported in six publications. Only one study, which had several problematic issues discussed in the document, did not find an effect on mammary gland development.

The studies of mammary gland development from peripubertal exposure are also presented in great detail. As discussed, it is not unexpected that effects differ from exposures during different lifestages. Additionally, problematic issues with the designs of the peripubertal studies that make interpretation of the results difficult are discussed in the document.

The statement in the comment that*: "As DWQI acknowledged, this is a highly uncertain endpoint, with limited support in the rodent toxicology literature and no clear link to human adverse effects"* is not accurate. The potential biological significance of the delayed mammary gland development caused by PFOA in mice is discussed in detail. The draft Health-based MCL Support Document (p. 125-128) includes a general overview of mammary gland development in rodents and the suitability of rodents as a model for human mammary gland development, as well as potential human health significance of effects on mammary gland development observed in rodents in general.

The citation of Macon et al. (2011) in these comments is not accurate, since Macon et al. (2011) did not evaluate reproduction and nursing capability. As discussed in the draft Health-based MCL Support Document (p. 132-134), the only study which evaluated nursing capability was White et al. (2011b). It is not true that the draft Health-based MCL Support Document does not "disclose" that effects were not observed on body weight of offspring of dams who had earlier developmental exposure to PFOA in White et al. (2011b). For reasons provided in the document, including that effect on ability to provide nutritional support to offspring has been evaluated in only one study, the Health Effects Subcommittee concluded (p. 132) that "the available toxicological information is not sufficient to make conclusions about the effects of developmental exposure to PFOA on lactational function." Also, as noted in the draft Health-based MCL Support Document (p. 133), possibly relevant to this issue, the two human studies (Fei et al., 2010; Romano et al., 2016) that were available both suggest that maternal exposure to PFOA may be related to shorter duration of breastfeeding. An additional more recent study that reported similar results has been added to the final document (Timmermann et al., 2016. Reprod. Toxicol., in press). A recent article (Konkel. 2017. Env. Health Perspect. 125 (1): A17-A23) notes that these three studies with similar observations in populations from different nations has led some researchers to conclude that there might be a link to effects on mammary gland development and/or maternal metabolism.

As discussed in the draft Health-based MCL Support Document (p. 128-132), developmental exposure to PFOA consistently caused delays in mammary gland development, as indicated by structural changes observed through microscopic evaluation of whole mounts of

mammary glands. In the only study in which developmentally exposed mice were followed through adulthood, histological changes in the mammary glands persisted until adulthood and were considered permanent. Delayed mammary gland development occurs in a dose-related fashion, and there is no information indicating it is not relevant to humans. As discussed in the draft Health-based MCL Support Document (p. 126), several researchers conclude that effects on the mammary gland such as those observed from developmental exposures to PFOA may relate to increased risk of breast cancer later in life, although no information specific to PFOA is available on this question. For these reasons, delayed mammary gland development is considered an appropriate endpoint for consideration in development of the risk assessment. As discussed above, based on currently available data, the Health Effects Subcommittee concluded that this endpoint is most appropriately considered through application of an uncertainty factor used to account for "concern that future studies may identify a more sensitive effect, target organ, population, or lifestage."

COMMENT: "*DWQI derived a far lower PFOA MCL of 14 ppt by citing the work of Post et al. (2012). However, the Post et al. (2012) review manuscript would not meet most jurisdictions' quality standards, such as USEPA standards, for acceptance if it was conducted by industry. The Post et al. (2012) study fails to demonstrate any dose/response relationship in the reported data tables, and repeats data already summarized by the USEPA (2016) document. For most of the original studies reviewed, group sizes are far too small (i.e. the Macon et al. 2011 data set had n = 3 to 5 measurements of mammary glands per exposure group) to conclude a biological effect. When USEPA finalized its PFOA review in 2016, it did not find the Post et al. (2012) paper informative, as all key (original research) studies cited by Post et al. (2012) had been included in the USEPA prior assessment document."* (Chemistry Council of NJ)

RESPONSE: The intent of this comment is unclear. Post et al. (2012) is a review of the human and animal health effects literature on PFOA, and includes Benchmark Dose (BMD) modeling of two parameters of delayed mammary gland development. Post et al. (2012) was cited to indicate that the BMDs for mammary gland development in the DWQI document had been previously published. However, the publication of these BMDs is not essential or necessary for their presentation in the DWQI document. The BMDs are based on data from Macon et al. (2011). There was a clear dose-response for both of the parameters of mammary gland development from Macon et al. (2011) that were modeled in Post et al. (2012), with statistical significance for one of the parameters at all dose levels, including the lowest dose. The data for both parameters are appropriate for dose-response modeling, based on the criteria for statistical significance specified in USEPA Benchmark Dose Technical Guidance (2012).

COMMENT: *In addition, the individual studies on mammary gland developmental delays often had significant weaknesses, such as lack of statistical adverse effects "due to interindividual variance and multiple criteria used to calculate mammary gland development scores".* (Chemistry Council of NJ)

RESPONSE: This comment misstates both the source and the intended meaning of the quoted statement. The commenter incorrectly attributes the quoted statement to Macon et al. (2011). However, this statement is from p. 3-93 of USEPA (2016b) and is presented out of context by the commenter. USEPA (2016b) includes this phrase in its discussion of effects of PFOA on mammary gland development in the cross-fostering study of White et al. (2009). This study includes groups exposed in utero, through lactation, or both; multiple doses; and assessments at multiple time points (3, 6, and 9 weeks of age). USEPA (2016b) discusses that effects were observed at almost all doses and time points, but that one dose group did not differ from controls at 6 weeks of age, possibly *"due to interindividual variance and multiple criteria used to calculate mammary gland development scores."* Additionally, abnormal foci were present in adulthood (18 months of age) in mammary glands of mice exposed to PFOA only early in life.

5. Selection of Uncertainty Factors

COMMENT: *"…Instead the Subcommittee arbitrarily applied an additional 10 UF to an unrelated endpoint (increased liver weight that forms the basis for their MCL derivation) to compensate for the more sensitive endpoint (delayed mammary gland development). This is confusing. Why not use the more sensitive endpoint for which adequate toxicity data already exists, including a BMDL, even if that endpoint has not previously been used, versus adding an additional uncertainty factor to an alternate endpoint to compensate for an uncertainty that is, in fact, known?* (Delaware Riverkeeper Network)

RESPONSE: This comment is addressed under "Consideration of mammary gland effects" on p. 19 above. In summary, the Health Effects Subcommittee decided not to use this endpoint as the primary basis for the quantitative risk assessment, in large part because there is no precedent for doing so. It was also noted that the permanent histopathological changes in adulthood observed in mammary glands of developmentally exposed offspring were looked for in only one study. Additionally, only limited data are available regarding the effects of developmental exposure to PFOA on lactational function. Only a single study assessed this endpoint in mice, and this study did not observe a decrease in body weight of offspring nursed by dams with earlier developmental exposure. If additional future studies continue to support these findings, then this endpoint could be reconsidered for use as the basis for quantitative risk assessment.

COMMENT: (In regard to the inclusion of a UF for low dose developmental effects) *"…basing a regulatory action on this endpoint in a highly variable species (mice) is, as DWQI acknowledged, not done by other jurisdictions."* (Chemistry Council of NJ).

RESPONSE: This comment is not accurate. The draft DWQI document does not "acknowledge" that mammary gland development was not considered in risk assessments developed by "other jurisdictions". Although PFOA drinking water risk assessments conducted by other states are not discussed in detail in the DWQI document, primarily because most of them are currently under revision, it should be noted that the Maximum Exposure Guideline for PFOA in Drinking Water developed by the Maine Dept. of Health and Human Services (2014) includes a UF of 10 to account for delayed mammary gland in mice, as well as potential immune effects in humans, at much lower doses than the endpoint (increased liver weight) used as the primary basis for the risk assessment. (Maine DHHS, 2014. https://www1.maine.gov/dhhs/mecdc/environmental-health/eohp/wells/documents/pfoameg.pdf)

Also, as noted below, the UF accounts for low-dose developmental effects in general, not just delayed mammary gland development. These effects include persistent hepatic toxicity after developmental exposure and other endpoints.

COMMENT: "*DWQI derived a far lower PFOA MCL of 14 ppt than the federal guideline by using only professional judgment to add an additional "safety factor" to account for possible mammary gland developmental effects that could occur at much lower doses than those that caused increased liver weight relied upon in the USEPA risk assessment resulting in the federal 70 ppt guideline for PFOA. Notwithstanding the weaknesses within the possible mammary gland evidence itself, …, the application of somewhat arbitrary "safety factors" would have impacts on NJ citizens …, and is not supported or borne out by the human evidence. Species differences explain why the DWQI conservatism is not necessary, and NJ citizens and water purveyors would be held to a more stringent … standard than the science supports as necessary."* (Chemistry Council of NJ).

RESPONSE: The basis of this comment is incorrect. The USEPA Health Advisory for PFOA (USEPA, 2016a; "federal 70 ppt guideline") is not based on increased liver weight. It is based on developmental effects in mice (delayed ossification and accelerated puberty in males). However, as discussed above, other developmental effects, including delayed mammary gland development and persistent hepatic toxicity, occurred at lower doses than those causing increased liver weight or the developmental effects used by USEPA (2016a).

The inclusion of this uncertainty factor is not "arbitrary" or based primarily on professional judgement. The uncertainty factor was included because current USEPA risk assessment

guidance states that an uncertainty factor should be applied "if there is concern that future studies may identify a more sensitive effect, target organ, population, or lifestage." See: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1037tr.pdf The toxicological database for PFOA indicates a need for concern for developmental toxicity, including delayed mammary gland development and persistent hepatic toxicity, that occur at doses well below those that cause increased liver weight, the primary basis of the Reference Dose developed in the draft Health-based MCL Support Document (p. 214).

Additionally, the need for this UF is supported by the human evidence, in contrast to the statements of the commenter. Inclusion of the UF is supported by the serum PFOA levels that result from exposure to drinking water contaminated with PFOA in comparison to the serum PFOA levels associated with human health effects. Based on these considerations, the Health Effects Subcommittee definitively concludes that the inclusion of this UF is appropriate and consistent with USEPA risk assessment guidance, and that the resulting Health-based MCL is not overly stringent.

COMMENT: *If, overall, the underlying scientific data related to mammary gland development is insufficient and not robust enough to be the basis of a regulation, then forcing an additional uncertainty factor to be applied to account for the endpoint is not scientific or logical."* (Chemistry Council of NJ)

"An extra uncertainty factor of 10 was applied to account for potential developmental toxicity; however, this factor should be removed given the weak evidence for developmental toxicity. Each uncertainty factor applied by DWQI results in a lower MCL. DWQI applied an extra uncertainty factor of 10 to account for potential developmental effects in humans. DWQI based the decision on a PFOA study in rodents in which delayed mammary gland development was observed following perinatal exposure. … Not only does consideration of possible PFOA-mediated developmental effects result in a lower MCL recommendation by the unwarranted extra uncertainty factor, the classification of PFOA as a developmental toxicant contributes to the public's unsupported concern for increased risk for women of childbearing age and infants. DWQI should remove this unnecessary uncertainty factor." (Chemistry Council of NJ; Note: The parts of these comments stating that developmental toxicity of PFOA is not well established, and about use of mammary gland effects as a relevant toxicological endpoint, were addressed on p. 8 and p. 21-14 above but are included again here to provide context for the comments.)

RESPONSE: The uncertainty factor of 10 mentioned in the comment is included to protect for low-dose developmental effects that are not otherwise accounted for in the risk assessment. As discussed in the draft DWQI document, these effects include not only delayed mammary gland development but also persistent liver toxicity from developmental

exposure.

As above, according to current USEPA risk assessment guidance, an uncertainty factor should be applied "if there is concern that future studies may identify a more sensitive effect, target organ, population, or lifestage." See: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1037tr.pdf The toxicological database for PFOA indicates a need for concern that developmental toxicity, including delayed mammary gland development and persistent hepatic toxicity, occur at doses well below those that cause increased liver weight, the primary basis of the Reference Dose. The Reference Dose based on delayed mammary gland development of 0.11 ng/kg/day supports an MCL of 0.77 ng/L (using default exposure assumptions). Persistent hepatic toxicity from developmental exposure occurred at similarly low doses as delayed mammary gland development, although the serum PFOA data needed for dose-response modeling for RfD development are not available for this endpoint.

Although the Health Effects Subcommittee decided not to use the RfD for delayed mammary gland development as the primary basis of the quantitative risk assessment, it definitively concludes that an additional uncertainty factor is needed to protect for the low dose developmental effects mentioned above, and that the inclusion of the additional UF does not result in an unreasonably low Health-based MCL. It is noted that the recommended Health-based MCL of 14 ng/L is 18-fold higher than the Health-based MCL of 0.77 ng/L supported by the Reference Dose for delayed mammary gland development. If the additional UF were not included, the Health-based MCL would be 140 ng/L, well above the drinking water concentrations that have been associated with human health effects. Based on these considerations, the Health Effects Subcommittee concludes that the inclusion of this UF is appropriate and consistent with USEPA risk assessment guidance, and that the resulting Health-based MCL is not overly stringent.

CANCER RISK ASSESSMENT

1. Uncertainties and limitations of quantitative cancer analysis

COMMENT: *"DWQI should thoroughly discuss the uncertainties and limitations in their quantitative cancer analysis.*" (Chemistry Council of NJ)

RESPONSE: The uncertainties in the quantitative cancer risk assessment in the draft Health-based MCL Support Document are similar to those for quantitative cancer risk assessments for other environmental contaminants that are based on animal data. The document notes on p. 221 that "uncertainties about the human relevance of effects seen in animals are inherent to all risk assessments based on animal data." As discussed in the Mode

of Action section of the document (p. 198-199), available data indicate that the testicular tumors that were modeled are relevant to humans for the purposes of risk assessment. The uncertainties related to extrapolation to the one-in-one million lifetime cancer risk level from the higher rates of tumor incidence in the study that was used are also inherent to all cancer risk assessments based on animal data. The uncertainties related to human-to-animal extrapolation are reduced by the use of an approach that compares humans to animals on the basis of internal dose, rather than administered dose.

2. Carcinogenicity classification

COMMENT: *"DWQI significantly overstated the link between PFOA exposure and carcinogenicity in humans and failed to rely on the most recent comprehensive assessments of the available science."*

"Despite significant evidence demonstrating no link between human exposures to PFOA and cancer, DWQI summarized the positive studies and ignored conflicting evidence and limitations of studies that do not support DWQI's conclusions."

"Although the cancer endpoint was not explicitly used to derive the draft MCL, DWQI's cancer discussion for PFOA could contribute to the overall narrative of PFOA as a "cancer causing chemical" in the public perception. We recommend that DWQI provide a more fair and balanced analysis of PFOA potential carcinogenicity, which would lend to the conclusion that there is not a causal association between PFOA exposure and cancer in humans (see also Chang et al. 2014)." (Chemistry Council of NJ)

RESPONSE: The draft Health-based MCL Support Document did not state that a causal connection between PFOA and human cancer has been established, and it did not use human epidemiology data as the basis for quantitative risk assessment. Additionally, as noted, the quantitative risk assessment based on animal tumor data is not the primary basis for the Health-based MCL, but rather supports the risk assessment based on non-cancer endpoints.

The draft Health-based MCL Support Document (p. 82-83) discusses the conclusions regarding weight of evidence for human carcinogenicity by several authoritative bodies (USEPA Science Advisory Board, USEPA, and IARC, which is part of the World Health Organization). The Health Effects Subcommittee notes that the final IARC (2016) monograph on PFOA became available after the draft DWQI document was written. The final DWQI document cites the IARC (2016) monograph rather than the shorter 2015 summary cited in the draft DWQI document. The epidemiological studies (positive and negative) that IARC (2016) relied on for its conclusions regarding evidence for cancer in humans are summarized in cancer epidemiology section of the final Health-based MCL

Support Document.

COMMENT: "*DWQI cites the IARC cancer evaluation for PFOA, despite the shortcomings of IARC's antiquated classification scheme noted by international scientists, and did not consider the recent Health Council of the Netherlands evaluation that concluded that the data are insufficient to make any conclusions regarding the carcinogenicity of PFOA and its salts."*

"Importantly, IARC has recently come under attack from international scientists for their antiquated and inaccurate cancer assessments that do not include a weight-of-evidence approach, do not include all relevant regulatory studies, and that cause unnecessary health scares in the public (Boobis et al. 2016). We recommend a more balanced and fair evaluation of the PFOA carcinogenicity data, taking into consideration the evaluation of the Health Council of the Netherlands (Health Council of the Netherlands 2013), using a true weight-of-evidence analysis, and using only authoritative and recent regulatory references." (Chemistry Council of NJ)

The commenter cites a recent commentary (Boobis et al., 2016) that discusses the need to incorporate both risk-characterization and hazard identification into carcinogenicity evaluations; it notes that IARC's cancer classifications are based only on hazard identification. *De novo* evaluation of human carcinogenic potential was not performed or presented in the Health-based MCL Support Document. Instead, the document summarizes the conclusions made by several authoritative bodies regarding carcinogenicity classification. As discussed in the draft Health-based MCL Support document, PFOA has been classified as a likely carcinogen by the USEPA SAB (2006) and a suggestive carcinogen by USEPA Office of Water (2016a). According to USEPA (2005) Guidelines for Carcinogen Risk Assessment followed by the DWQI, a cancer potency slope factor is developed for both suggestive and likely carcinogens if the mode of action is considered relevant to humans and data to support slope factor development are available.

The commentary by Boobis et al. (2016) also emphasizes the need to consider mode of action information related to carcinogenicity. The DWQI document provides a thorough discussion of mode of action data for carcinogenicity of PFOA, supporting the conclusion that each of the three types of tumors caused by PFOA in toxicological studies should be considered relevant to humans under USEPA risk assessment guidance.

The commenter also suggests that the DWQI rely on the Health Council of the Netherlands (2013) assessment of PFOA. As discussed in response to a comment above, the Health Council of the Netherlands relies on IARC assessments when possible. However, the Health Council of the Netherlands PFOA evaluation was written in 2013, and thus did not consider

the more recent IARC (2015) conclusion that PFOA is possibly carcinogenic to humans.

Additionally, as stated above, the Health Effects Subcommittee notes that the criteria used by the Health Council of the Netherlands to determine the carcinogenicity classification are different from those used by USEPA, NJDEP, and the DWQI. See https://www.gezondheidsraad.nl/sites/default/files/A1007_0.pdf.

COMMENT: *"… DWQI highlighted the outdated and unofficial EPA Science Advisory Board (SAB) conclusions from 2006, over the more recent EPA Office of Water cancer description (USEPA 2016). All references to the EPA SAB report should be deleted. The SAB report is not a peer-reviewed final report representing EPA positions. Furthermore, it is not the most recent EPA evaluation of PFOA carcinogenicity and it is disingenuous to continue to reference this document and diminish the more recent and peer-reviewed EPA Office of Water Health Advisory document (USEPA 2016), which followed the same EPA cancer guidelines (USEPA 2005).* (Chemistry Council of NJ)

RESPONSE: The Health Effects Subcommittee disagrees with this comment and notes that it contains statements that are not factually accurate. The conclusions about PFOA carcinogenicity by both the EPA SAB (2006) and the EPA Office of Water (2016) are presented in the DWQI document. From the draft DWQI document (p. 82): "More recently, the USEPA Office of Water (2016a) concluded that PFOA has suggestive evidence of carcinogenic potential for PFOA based on the human studies mentioned above that found an association of serum PFOA with kidney and testicular tumors in communities with drinking water exposure and increased incidence of tumors in one or more organs in two chronic rat bioassays."

The EPA SAB (2006) report presents the conclusions of a panel of prominent scientists selected for their expertise relevant to the topics being evaluated. Since the role of an SAB is to serve as peer reviewers to EPA, SAB reports do not undergo further peer review. The SAB report is a final document and is not "unofficial." It was finalized by the SAB and forwarded to the EPA Administrator. It is notable that the EPA SAB concluded that PFOA is a likely human carcinogen based on toxicological studies and limited mode of action data, prior to the availability of later human studies that found an association of PFOA with cancer and additional mode of action data that support the earlier mode of action studies.

3. Interspecies extrapolation in cancer risk assessment

COMMENT: "*In addition, DWQI derives a human equivalent dose from an administered dose in rats (Butenhoff et al. 2012), rather than a study that reports the internal dose (serum PFOA). This is inconsistent with the data usability criteria applied by DWQI for non-cancer*

studies (pg. 205-206): "Only those studies that provide serum PFOA data were considered for dose-response modeling for non-carcinogenic effects. A risk assessment approach based on measured serum PFOA levels is less uncertain than one based on pharmacokinetic modeling of estimated serum PFOA levels or an approach in which interspecies extrapolations is based on interspecies half-life differences." (Chemistry Council of NJ)

RESPONSE: For both non-cancer and cancer risk assessment in the draft Health-based MCL Support Document, animal-to-human comparisons were made on the basis of internal dose, rather than administered dose, as is generally accepted as appropriate for risk assessment of PFOA. For non-cancer risk assessment, PFOA serum data from the end of the dosing period were available for key endpoints, and the interspecies comparison used these data. The use of serum PFOA data from the animal studies is most important for the studies of non-cancer endpoints, since some of the studies evaluated were of relatively short duration and steady-state serum PFOA levels may not have been reached. As explained in the draft Health-based MCL Support Document (p. 219-220), serum PFOA data were not available for the chronic study used in the cancer risk assessment, and the ratio of human to rat half-lives was used to compare body burdens. In such a chronic study, the possibility that steady-state has not been reached is not an issue.

Use of the ratio of human-to-animal half-lives is a valid approach for accounting for interspecies toxicokinetic differences that has been used in other risk assessment of PFOA, including the USEPA Provisional Health Advisory (2009). See https://www.epa.gov/sites/production/files/2015-09/documents/pfoa-pfos-provisional.pdf.

Please note that a half-life of 7 days specific to the strain of male rats in the chronic cancer study was located in the literature and was used, as explained on p. 220 of draft Health-based MCL Support Document. This value is longer than the generally available half-life values for male rats of 4-6 days provided in numerous review articles. Also, the human half-life of 2.3 years is the shortest human half-life for PFOA reported in the literature. The use of a longer half-life for rats and a shorter half-life for humans results in a less stringent risk assessment than if a shorter rat half-life or a longer human half-life had been used.

EXPOSURE ASSUMPTIONS

1. Use of water ingestion rate for children instead of adults

COMMENT: *"Alternatively, we calculate a MCL of 6 ng/L for children group ages 1-6 using the increased liver weight endpoint, with exposure values we determined for mean weight and 90th percentile water intake in that group. Children therefore represent a special case. They have greater drinking water and food consumption on a body weight basis. Using*

adult default exposure values is inappropriate since a priori use of adult default values for body weight and water intake omits protection to children, the population's most vulnerable exposure group. Calculation of a MCL using adult default values results in a RfD to children (age group 1-6) that significantly exceeds that deemed allowable by NJDWQI based on the increased liver weight toxicity endpoint." (Delaware Riverkeeper Network; Note: Commenter included detailed basis for calculation of the value mentioned above.)

RESPONSE: It is acknowledged that infants and children have higher exposures to PFOA from breast milk or contaminated drinking water than adults. However, the Health Effects Subcommittee did not develop the Health-based MCL using exposure factors for infants or children because of uncertainties related to toxicokinetic considerations. Specifically, it is not clear that the higher exposures of infants and children can be used with an RfD based on a steady-state serum level. Steady-state is reached from exposure to a constant dose over a period of many years. In contrast, the higher exposure rates in infants and children vary at different age periods and occur over a time period shorter than needed to reach steady-state. As discussed in the DWQI document, use of a Relative Source Contribution (RSC) factor of 20%, while not explicitly intended for this purpose, also at least partially accounts for the higher PFOA exposures in young infants, the age group expected to have the highest exposure.

2. Selection of Relative Source Contribution factor

COMMENT: "*One study found that drinking water (at 9.66 ng/l) represented 24% of total exposure (Thompson et al 2011). Using NHANES 2003/2004 data, Lorber and Egeghy also determined a relative contribution of drinking water to total intake at 24%. They note that this rate is similar among adults and children (Lorber and Egeghy 2011). Others have found that drinking water represents a much higher portion of total exposure (Noorlander et al. 2011). A 20% contribution to total intake is used as a default value for relative source contribution (RSC) in this risk analyses."* (Delaware Riverkeeper Network)

RESPONSE: This comment is acknowledged. The data presented by Lorber and Egeghy (2011) provide additional support for use of the default Relative Source Contribution factor of 20%, in addition to the justification provided in the comment below. It should be noted that, by convention, Relative Source Contribution factor values are rounded to one significant figure.

COMMENT: *"… the very same publication used by DWQI to support the PFOA clearance factor, Lorber et al. (2011), provides data to support a RSC of between 60 and 70 percent. It is illogical for DWQI to utilize data from Lorber (2011) for a parameter that impacts the health-based MCL by over 100 fold (i.e. the clearance factor), and not use this same*

publication and data therein to support a PFOA-specific RSC." (Chemistry Council of NJ)

RESPONSE: The commenter appears to misunderstand how the information presented in the cited study ("Lorber, 2011", i.e. Lorber and Egeghy, 2011) would be used as the basis for selection of a Relative Source Contribution (RSC) factor. As noted in the comment from the Delaware Riverkeeper Network above, Lorber and Egeghy (2011) state that "the relative contribution [from ingestion of drinking water] to total intake (about 24%) is similar among adults and children." This means that about 76% of total intake comes from non-drinking water sources. The RSC represents the percent of total exposure from drinking water, not the percent of total exposure from non-drinking water sources. Therefore, the data presented in Lorber and Egeghy (2011) supports an RSC of 24% which rounds to 20%, the value used in the draft Health-based MCL Support Document (p. 217).

COMMENT: "*DWQI applies a default relative source contribution (RSC) of 20 percent, without considering the data available to support a PFOA-specific value, and despite having adopted a non-default value for PFNA."* (Chemistry Council of NJ)

"This decision is not scientific and is illogical and inconsistent. Not only is there sufficient information to derive a chemical-specific RSC, DWQI chose to adopt a non-default RSC of 50% for PFNA, despite significantly less PFNA exposure data than is available for PFOA. Available data strongly support a higher RSC, similar to the situation for PFNA. Some of the analysis conducted by DWQI in Appendix 2 can be used to demonstrate a higher RSC for drinking water exposure." (Chemistry Council of NJ)

RESPONSE: As discussed on p. 215 of the draft Health-based MCL Support Document, the Health Effects Subcommittee concluded that there are insufficient data to develop a chemical-specific RSC for PFOA and used the default RSC of 20%. There are no New Jersey-specific biomonitoring data for PFOA, and its frequent occurrence in NJ PWS suggests that its presence in other environmental media may also be greater in New Jersey than nationally. Therefore, New Jersey residents may also have higher exposure from non-drinking sources than the U.S. general population (e.g. NHANES). As discussed in the document, PFOA contamination in drinking water has been found in locations throughout NJ. Potential sources have been identified in some instances, while sources are unknown in other locations. In contrast, PFNA has been detected at substantial concentrations in NJ only in the vicinity of a likely industrial source.

Environmental contamination with PFOA that results in its presence in drinking water can also result in additional non-drinking water exposures. This contamination can arise from a sources that include releases to air, soil, and water from fluoropolymer telomer manufacturing facilities, on-site and off-site disposal from smaller industrial facilities that

make products from fluoropolymer dispersions containing PFOA, releases of aqueous firefighting foams, leachates from landfills, and land application of biosolids from wastewater treatment plants treating waste containing PFOA, among others. These various sources can potentially result in human exposures through contamination of nearby soils, house dust, or other environmental media. In communities with drinking water contamination, consumption of produce from home gardens or grown locally was associated with higher serum levels of PFOA (Emmett et al., 2006a; Holzer et al., 2008; Steenland et al., 2009a).

Additionally, the default RSC of 20%, while not explicitly intended for this purpose, also at least partially accounts for the higher PFOA exposures in infants. As discussed in detail in the draft Health-based MCL Support Document (p. 51-54, p. 216-217), exposures to infants, both breastfed and consuming formula prepared with contaminated drinking water, are several-fold higher than in than older individuals.

These higher infant exposures must be considered because the toxicological effects of concern (delayed mammary gland development and increased relative liver weight) occur from short term exposures relevant to elevated exposures in infancy, including when exposure occurs only via lactation.

HUMAN EPIDEMIOLOGY

1. **COMMENT: "***The document is cognizant that important human studies show consistent associations with several important biomarker outcomes, including but not limited to alterations of total and LDL cholesterol, and markers of immune response. These biomarker studies do not show "thresholds." Instead, the human dose-response curve for cholesterol and LDL cholesterol is asymptotic, meaning that most of the unfortunate "action" is at very low dose. (There are also effects at escalating doses, but there is correspondingly less increment with each log increase in dose, suggesting a possible saturation mechanism). The point is that low doses are likely to be physiologically quite active. The importance of this kind of association is underlined by the multiple efforts to find a noncausal reason for consistent association, such as to LDL and total cholesterol. Legitimate and important efforts to find a non-causal reason for the consistent association have been made, and no confounding or non-causal explanation has been found. The association is highly likely to be causal in humans. In addition, animal data now mirror these human findings, and have further suggested that dietary and physiology factors interact with PFOA to elevate cholesterol."* (Alan Ducatman)

RESPONSE: This comment is acknowledged. The Health Effects Subcommittee notes that associations with the human health effects mentioned in the comment have been reported in

the general population, whose exposures are from sources other than contaminated drinking water. For this reason, there is a need for caution for additional exposures from contaminated drinking water that will result in further increases in serum PFOA levels.

2. Variability in human serum PFOA measurement

COMMENT: *"…analyses of serum PFOA remain highly variable… The chemical/analytical precision and accuracy ascribed at low levels to water or serum in biomonitoring data often overshadow the tighter range of low-level biological responses. If accuracy of PFOA analyses is properly acknowledged to be less than 100% (for example, perhaps precise or accurate to only within +/- 30% of a true value) for serum, as compared to any given percent change in biological response (such as 5% for cancer or 10% for noncancer effect thresholds), the attempt to correlate analytical results to the DWQI-assessed candidate health effects is tenuous, at best. Thus, New Jersey should not be fooled into thinking that low-level analytical results are "true" and accurate when attempting to match water or serum PFOA to possible effects."* (Chemistry Council of NJ)

RESPONSE: The basis of this comment is not accurate for several reasons. First, the precision of the serum PFOA analytical results within the general population (e.g. NHANES) is reported to be 11% or lower (Calafat et al. 2007. Environ. Health Perspect. 115:1596-602), not 30% as hypothesized by the commenter. Second, the quantitative basis of the DWQI PFOA risk assessment is not based on data from human studies, as implied by the comment. Third, variability in serum PFOA measurements such as described in the comment would lead to non-differential exposure misclassification which can bias associations to the null (i.e., towards no association), rather than finding associations that do not actually exist. Exposure misclassification tends to produce biases towards missing associations when they actually exist, rather than finding associations when they do not actually exist. Finally, the precision and accuracy of analysis of water samples is not relevant to this point, because the associations in the human studies are based on serum PFOA levels, not drinking water concentrations.

3. Selection of sensitive endpoint

COMMENT: *"The criterion may be developed on the basis of epidemiologic evidence of a significant immunotoxic association in children… We calculate an approximate MCL of 0.5 ng/L based on the BMDL determined and the association found between immune suppression and serum PFOA levels in children as reported by Grandjean and Budtz-Jørgensen"*

The National Toxicology Program (NTP) supports a conclusion that PFOA alters human immune function (NTP 2016). A number of studies have shown PFOA immunotoxicity in that

PFOA suppresses immune response. Four studies assessing associations with antibody concentrations following vaccination had prospective study designs that allowed temporality assessment. Among these, a prospective birth cohort study in Norway found strong evidence of decreased rubella-induced antibodies with increasing PFOA maternal serum concentrations in 99 pregnant women with a subsequent follow-up of 56 children at 3 years of age (Granum et al. 2013). Although no statistically significant associations were found with responses to vaccines for Influenza Type B or Influenza Type A H1N1, a large prospective cohort study of 411 adults in the mid-Ohio valley found decreasing antibody concentrations following Influenza A H3N2 vaccination (Looker et al., 2014). A large prospective cohort of 656 consecutive singleton births in the Faroe Islands with prospective follow-up of 587 cohort members at ages 5 and 7 years, found a strong association between serum PFC concentrations (PFOA and PFOS) and serum antibody concentrations against tetanus and diphtheria toxoids (Grandjean and Budtz-Jørgensen 2013).

The NJDWQI report acknowledged that "data from other human studies and toxicology studies provides support for biological plausibility of decreased immune system response to vaccines in humans" (NJDWQI Report 2016). The Report cites Fletcher et al. (2009), which "reported several statistically significant associations between several markers of immune function (decreased IgA; decreased IgE in females only; increased anti-nuclear antibody; decreased C-reactive protein) and serum PFOA levels in communities with drinking water exposure to PFOA in a C8 Science Panel status report" (NJDWQI 2016).

NJDWQI notes that a "review of epidemiologic studies provides evidence of consistent findings among studies of decreased antibody concentrations following vaccination and PFOA. However, while there is epidemiologic evidence of temporality, evidence of an exposure-response is limited" (NJDWQI 2016). We disagree. We believe that where there is strong, significant epidemiologic evidence that includes quantitative data to enable derivation of a BMDL, such data should be taken into account in derivation of the MCL.

The Grandjean and Budtz-Jørgensen study represents the greatest sensitivity to PFOA thus studied, un-confounded by exposure to other chemical contaminants. In this study regression modeling of PFC concentrations (PFOA and PFOS) as independent variables along with potential confounders of sex, age, and booster type at age 5 and 7, with antibody concentrations as outcome, allowed determination of benchmark response (BMR) and benchmark dose (BMD).

The lower one-sided 95% CL (confidence limit) of the BMD, the BMDL (benchmark dose level), was determined in this study to be approximately 0.33 ng/ml for PFOA and 1.3 ng/ml for PFOS, based on the linear slope model of the regression. The study notes strong correlation between PFOS and PFOA, making mutual adjustment in the regression difficult.

However, in spite of this the BMDL developed does provide a strong epidemiologic basis to develop a MCL." (Delaware Riverkeeper Network)

COMMENT: *"However, we are concerned that the DWQI proposed level, even though considerably lower than the U.S. EPA PFOA health advisory, exceeds a previously estimated threshold protective of PFOA-associated immunotoxicity (Grandjean et al., 2015). A number of peer-reviewed studies suggest adverse human health effects at the current exposure levels. These findings include:*

- *Decreased antibody response associated with PFOA exposure (DeWitt et al., 2012; DeWitt et al., 2016)*
- *Inverse association of serum-PFOA concentrations with the response to booster vaccination in children and adults (Looker et al., 2015, Kielsen et al., 2016; Grandjean et al., 2012)*
- *Shorter breastfeeding duration in women with higher serum-PFOA concentrations (Timmermann et al., 2016 (in press), Romano et al., 2016)*
- *Positive association between maternal serum-PFOA concentration at childbirth and the number of episodes of common cold and gastroenteritis in children (Granum et al., 2013)*
- *Association of prenatal PFOA exposure in the high- compared to the low-tertile with a statistically significant increased odds of experiencing days with fever above the median at age (Dalsager et al., 2016).*
- *Association of adverse birth outcomes (e.g., decreased birth weight) with serum PFOA concentrations during pregnancy (Whitworth et al., 2012)."* (Green Science Policy Institute)

COMMENT: Some selected language: *"…a vaccination constitutes a natural and highly feasible experiment of antigen exposure, where the same dose of antigen is applied at the same age at exposure, so that the antibody response can be ascertained by a routine assay and where the outcome is of clinical relevance. We have therefore carried out extensive studies of children exposed to PFOA and related compounds. Our findings and those reported by other colleagues show an inverse association of serum-PFOA concentrations with the response to booster vaccination in children and adults, thus suggesting a deficit in the reactivation by T cells of B cells in the germinal centers, thereby resulting in B cells becoming less effective with respect to antibody production. These findings are supported by in vitro studies, but the mechanisms are unclear (Page 2-3) … Our own study suggested that serum-PFAS concentrations at age 5 years were associated with increased odds of asthma only among the children who had not yet been vaccinated against measles, mumps, and rubella (MMR), while the association was reversed among MMR-vaccinated children...From our study published in JAMA, I would like to emphasize that several children at age 7 years (two years after the age-5 diphtheria and tetanus vaccination booster) had an antibody against diphtheria and/or tetanus below the clinically protective level of 0.1 IU/mL. This*

means that the children had no long-term protection against the diseases despite a total of four vaccinations. We calculated the odds ratios (ORs) for a doubling in the child's age-5 serum-PFOA concentration as a predictor of having an antibody concentration below the 0.1 UI/mL at age 7 years. The ORs for tetanus was 4.2 (95% CI, 1.5-11.4) and for diphtheria 3.3 (95% CI, 1.4-5.5) …. When we used structural equation model that allowed us to combine the two serum-PFOA measurements at ages 5 and 7 years, we found that a doubled serum-PFOA concentrations was associated with a change in the age-7 antibody concentration of -38.2% (95% CI: -56.1, -13.0) for tetanus and -34/7% (95% CI: -52.5, -10.2%) for diphtheria. When we adjusted for the other PFASs, the regression coefficients were -296% and -26.9%, respectively, i.e., virtually unchanged. Likewise adjustment for the elevated PCB exposure in the Faroes did not materially affect the calculations.

These findings support the notion that PFOA has an independent immunotoxic effect, which is in accordance with the data from the animal experiments referred to above. Still, the human evidence relies on serum-PFOA measured at two postnatal ages and does not take into account the possible effects of immunotoxicity occurring during potentially more vulnerable ages in early postnatal life (i.e. infancy). Thus, the reported associations may underestimate the toxicity at younger ages.

… Our observation that PFOA effects may be distinguished from effects of other PFASs probably relative to the fact that PFOA in the Faroese population correlated less closely with the co-exposures, thereby allowing mutual adjustment.

…Some of our calculations have shown decreases in antibody concentrations of up to about 50% at a doubled PFAS exposure. These decreases are not trivial, and effects of such magnitude would otherwise be expected only with exposures to such factors as ionizing radiation and certain cancer drugs."

…Key references are referred to by numbers in the above text and are listed below"
(Philippe Grandjean)

RESPONSE: In consideration of the comments regarding use of human epidemiology in general, and in particular recommendations to use an epidemiologic study of serum PFOA and immune response (Grandjean et al., 2012) for quantitative risk assessment, the Health Effects Subcommittee revisited its evaluation of both Grandjean et al. (2012) and other epidemiologic studies of PFOA and immune response following vaccination. The Subcommittee also evaluated other contaminants for which human epidemiology studies of non-cancer endpoints were used as the basis for quantitative risk assessment.

Grandjean et al. (2012) is a prospective birth cohort study which evaluated the impact of

PFOA serum concentrations on antibody response following vaccination among children at birth and at follow-up at 5 and 7 years of age in the Faroe Islands. There are some aspects of Grandjean et al. (2012) that may limit its applicability for use in quantitative risk assessment. In particular, the strong correlation between PFOS and PFOA limited the researchers' ability to mutually adjust for both, thereby preventing inference in regard to causal attribution to a specific compound. The commenters have suggested that, in spite of this limitation, this study is sufficient for use as the basis for quantitative risk assessment. Although we are in agreement about the value of Grandjean et al. (2012) for hazard identification and to provide support for a protective approach based on toxicological data, we remain tentative regarding its use as the basis for quantitative risk assessment.

In addition to Grandjean et al. (2012), two other studies (Granum et al., 2013, and Kielsen et al., 2015) evaluated associations between serum PFOA concentrations and antibody concentrations following vaccination. Granum et al. (2013) collected blood samples at delivery from 99 pregnant women with a subsequent follow-up sample of 56 children at 3 years of age. These investigators found strong evidence of decreased rubella-induced antibodies with increasing PFOA maternal serum concentrations, but associations with PFOA and responses to tetanus, measles, and influenza vaccines were not statistically significant. The median exposure range in Granum et al. (2013) is lower than the exposure range in Grandjean et al. (2012), 1.1 ng/ml and 4.1 ng/ml respectively. In Kielson et al. (2015), a prospective cohort of 12 adults recruited from hospital staff in Denmark with median serum PFOA concentration of 1.7 ng/ml found no statistically significant associations with antibody response to tetanus or diphtheria vaccines.

Associations between decreased antibody concentration and increasing PFOA concentration may be related to a threshold such that limited evidence of associations was found among the two studies with median serum PFOA concentrations below 2 ng/ml (Granum et al, 2013 and Kielsen et al., 2015). Both of these studies also had small sample sizes which may have restricted the power of the study to detect a statistically significant decrease. However, there remain a limited number of comparisons across the same vaccination types and inconsistency across studies evaluating the same vaccine responses.

When used as the primary basis for quantitative risk assessment, the database of epidemiologic evidence for a health endpoint must be robust and provide substantive evidence of a causal relationship. Contaminants for which human epidemiology studies of non-cancer endpoints is used as the basis for quantitative risk assessment include 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; i.e. "dioxin"), methylmercury, lead, and ozone. For each of these compounds, the human health effects are well established through health effects observed from high-dose exposures in human populations, experimental exposure studies, and/or decades of consistent epidemiologic findings across diverse populations. The

epidemiologic database for these compounds generally exhibit strength, consistency, temporality, biological gradient, and plausibility and therefore represent the high bar required for use in quantitative risk assessment.

In summary, as the commenters have stated, sufficient quantitative data are available in Grandjean et al. (2012) for use in benchmark dose modeling, as demonstrated in Grandjean et al. (2013). The Health Effects Subcommittee acknowledges the significance of Grandjean's work and generally supports the use of epidemiologic studies in quantitative risk assessment. However, due to the observational nature of human epidemiology, there is a high bar for its use as the basis for quantitative risk assessment, and the Health Effects Subcommittee maintains that the epidemiologic database is insufficient to support the use of decreased vaccine response as the basis for quantitative risk assessment of PFOA. Although the database for antibody response following vaccination is currently not conclusive enough to use as the primary basis for risk assessment, it supports the need for a protective approach in the risk assessment based on animal data. If future studies provide additional support for a relationship between PFOA and decreased response to vaccinations, particularly in infants and children, then this endpoint could be reconsidered for use as the basis for quantitative risk assessment.

4. Human data for liver effects

COMMENT: *" Additionally, we maintain that the existing data do not clearly link low-level human exposures to PFOA-mediated adverse liver effects in humans. There have not been consistent associations of PFOA with liver biomarkers or liver changes in human studies, including those with serum concentrations equivalent to and much greater than levels used to calculate the proposed MCL. Data from studies of workers with high exposures to PFOA have not demonstrated evidence of increased liver disease and data on liver enzyme parameters have been inconsistent (for example, see Leonard 2003; Sakr et al. 2007; Leonard et al. 2008; Lundin et al. 2009; Steeland [sic] and Woskie, 2012)."* (Chemistry Council of New Jersey)

RESPONSE: As discussed in the DWQI document, there is consistent evidence supportive of a causal relationship for hepatic effects of PFOA, as indicated by increased serum levels of the liver enzyme ALT, in subjects with general population level exposures and in communities with higher exposures from contaminated drinking water. The potential reasons that results of studies of highly exposed workers may be inconsistent are discussed in the DWQI document. The steepest dose-response for associations of PFOA with some health endpoints, including increased serum levels of liver enzymes, has been observed within the lower range of serum PFOA concentrations. Studies of highly exposed workers may not include a sufficient number of individuals within these low level exposure ranges to serve as

a comparison group, and thus may not detect associations with exposure that are actually present. While the available studies did not find an association of PFOA with liver disease, the epidemiologic evidence for this endpoint is limited since it was evaluated in only a few studies.

The DWQI document notes that, although the magnitude of change for the parameters such as liver enzymes associated with PFOA is generally relatively small, these changes are of public health concern because population-level changes of this magnitude will result in a shift in the overall distribution of values such that the numbers of individuals with clinically abnormal values is increased.

5. Clinical trial of PFOA in advanced cancer patients

COMMENT: *"… we commend for your review… a controlled phase I clinical trial in humans, which, in simple terms, studied ammonium perfluorooctanoate (APFO), the ammonium salt of straight chain PFOA, as an anti-cancer treatment. The trial sought to determine a maximum tolerated dose in humans for further efficacy studies. The study involved weekly oral doses of APFO between 50 - 1,200 mg, which created blood plasma PFOA levels ranging from 30,000 – 600,000 ppb. At these extremely high levels, normal liver and kidney function were not affected. The study indicates that the human response to PFOA is significantly lower than that found in any of animal toxicology studies…"* (Chemistry Council of NJ comments submitted in response to 2014 DWQI request for additional technical information)

RESPONSE: The study cited in this comment (Macpherson et al., 2010) is not a peer-reviewed publication. It is the abstract of a poster "A phase I clinical trial of CXR1002 in patients with advanced cancer" presented at a scientific meeting (22nd EORTC – NCI–AACR Symposium on Molecular Targets and Cancer Therapeutics). The subjects in this study were 28 advanced cancer patients, median age 64.5, with different types of cancer. They were given doses of APFO of 50 to 750 mg once weekly for a median duration of 9 weeks. The blood plasma PFOA levels mentioned in the comment are not provided in the citation. The comment states that normal liver and kidney function were not affected. However, the abstract reports that one of the patients dosed with 600 mg weekly (about 1.2 mg/kg/day, assuming 70 kg body weight) experienced drug related toxicity (DLT) consisting of "grade 5 renal failure and transaminitis" (indicative of liver damage). These effects were noted as "possibly drug related" in the abstract. This study is of limited relevance to the Health Effects Subcommittee evaluation due to its subject group and design, as well as lack of peer review or availability of detailed methods, results, and conclusions. However, the Subcommittee notes that the information provided indicates the potential for PFOA to cause renal and hepatic toxicity in humans.

USEPA COMMENTS ON DWQI REVIEW OF USEPA DRINKING WATER HEALTH ADVISORY FOR PFOA

In May 2016, USEPA finalized Lifetime Drinking Water Health Advisories for PFOA and PFOS of 70 ng/L for each of these contaminants, and 70 ng/L for the total of these two contaminants. At the request of NJDEP, the Health Effects Subcommittee reviewed the USEPA PFOA Health Advisory and compared it to the DWQI Health-based MCL in Appendix 2 of the draft DWQI Health-based MCL Support document.

USEPA submitted comments to the DWQI regarding the Health Effects Subcommittee review of the USEPA PFOA Health Advisory. Summaries of the USEPA comments and the Health Effects Subcommittee responses are presented below.

1. General Comments

COMMENT: *USEPA notes that "states may choose to develop different HA or guideline values based on their own analyses, including more stringent values." USEPA also states that it is commenting only on the draft Appendix 2 of the DWQI Health Effects document (Comparison of USEPA Office of Water Health Advisory and DWQI Recommended Health-Based MCL for PFOA) and that "these comments are being provided to make clear the scientific basis described in the 2016 EPA lifetime HA for PFOA and are not intended to critique the NJ DWQI proposed value."*

RESPONSE: These comments are acknowledged.

2. Peer review of draft USEPA Health Advisory

COMMENT: *USEPA notes that an earlier 2014 draft of the health advisories underwent peer review, and that the final health advisories incorporate revisions based on comments from the peer reviewers and the public.*

RESPONSE: The DWQI notes that the USEPA Drinking Water Health Advisory for PFOA that was finalized in 2016 includes major changes (e.g. the endpoints used as basis for risk assessment) from the 2014 draft document that were not specifically reviewed by the peer reviewers. Also, the peer reviewers did not evaluate several of the major points brought up in the DWQI review of the USEPA Health Advisory (e.g. ability to predict increases in human serum PFOA level from drinking water exposures; consideration of animal-to-human half-life differences in the cancer risk assessment).

3. Toxicological endpoints used as basis for USEPA Health Advisory

COMMENT*: NJ DWQI stated that developmental effects in animal studies that occur at lower doses than the endpoints used as the basis for the RfD were not considered by USEPA. These include studies in which developmental exposures result persistent hepatic effects (Filgo et al., 2015; Quist et al., 2015) and delayed mammary gland development (Macon et al., 2011 and others).*

USEPA states that the "studies focused on liver effects by both Filgo et al. (2015) and Quist et al. (2015) are discussed extensively in EPA's HESD [Health Effects Support Document] for PFOA". They state that one of the major recommendations of the expert external peer review panel who reviewed EPA's draft HESDs was that EPA follow the criteria established by Hall et al. (2012) in the evaluation of the adversity of liver endpoints, and that EPA's assessment shows that liver weight and hypertrophy caused by PFOA do not meet the criteria for adversity. USEPA state that increased liver weight is acknowledged as a common finding of PFOA exposure, but not considered adverse in the absence of other effects as defined by Hall et al. (2012).

USEPA also states that delayed mammary gland development was not used as the critical effect for PFOA for several reasons, including ambiguity regarding the qualitative component of the scores and lack of observed effects on body weight of pups nursing from affected dams (White et al., 2011), and no differences in response to lactational challenge (White et al., 2011).

RESPONSE: The hepatic effects after developmental exposure reported by Filgo et al. (2015) and Quist et al. (2015) were not limited to the effects discussed by Hall et al. (2012) as not necessarily adverse (e.g. increased liver weight and hepatocellular hypertrophy such as are typically associated with enzyme induction or peroxisome proliferation). The hepatic effects reported in these studies included periportal inflammation and persistent mitochondrial damage (Quist et al., 2015) and bile duct hyperplasia and hematopoietic cell proliferation (Filgo et al., 2015). Therefore, Hall et al. (2012) do not provide a basis for dismissing these effects.

In regard to delayed mammary gland development, it is not clear what is meant by "ambiguity regarding the qualitative component of the scores" as a reason to dismiss consideration of this endpoint. Delayed mammary gland development from developmental exposures to mice was consistently reported in nine studies from five publications, and it was not reported in only one study that has multiple problematic issues discussed in the draft Health-based MCL Support Document (p. 130-132; Appendix 5, p. 89-91). Importantly, the Health Effects Subcommittee developed two separate Benchmark Doses which are almost identical for

different parameters related to mammary gland development, decreased number of terminal endbuds (a numerical parameter which is not subjective) and mammary gland development score (based on a number of parameters). As discussed in the draft Health-based MCL Support Document (p. 130), the Health Effects Subcommittee notes that structural changes in the mammary gland persisted to adulthood in the single study in which this endpoint was assessed, and that a structural change in an organ is a valid endpoint for risk assessment. The Health Effects Subcommittee also concluded that the available data are insufficient to make conclusions about whether lactational function is affected by PFOA.

COMMENT: *NJ DWQI stated that the long term consequences and functional significance of the effect on ossification in the Lau et al. (2006) study are unclear and thus question the use of this endpoint as the basis for the RfD for PFOA. NJ DWQI stated that the delayed ossification and puberty delay in Lau et al. (2006) are developmental delays and not adverse effects.*

RESPONSE: The review of the EPA Health Advisory presented in Appendix 2 of the draft Health-based MCL Support Document made the points mentioned in this comment in the context of the reasons USEPA provided for dismissing mammary gland development as an endpoint for risk assessment. **The point of the Health Effects Subcommittee's discussion of these issues is not to question the validity of these endpoints (delayed ossification and accelerated puberty) as the basis for risk assessment in general. Rather, the Subcommittee intends to convey that the reasons provided by USEPA for dismissing consideration of delayed mammary gland development do not appear to be valid and that they also apply equally to the endpoints used by USEPA.**

A primary basis for USEPA's rationale for dismissing delayed mammary gland development is that its functional significance is unclear. The Health Effects Subcommittee concludes that the functional significance of the endpoints used by USEPA (delayed ossification and accelerated male puberty) is also unclear. Because the phalanges appeared to develop normally in similarly dosed mice from the same study that were not sacrificed at term and were followed during the postnatal period (personal communication with C. Lau), the functional significance of the delayed ossification observed in the fetuses sacrificed at term is unclear. Similarly, the functional significance of accelerated puberty is unclear

COMMENT: *Significantly increased limb deformations at birth for doses ≥ 5 mg/kg/day suggest that the effects at the lower doses are more than simple developmental delays.*

RESPONSE: As above, it is emphasized that the Health Effects Subcommittee **does not question the validity of delayed ossification as an endpoint for risk assessment**, but rather points out that the same reasons provided by USEPA for dismissing delayed mammary gland

development do not appear to be valid and also apply to delayed ossification. However, the Health Effects Subcommittee notes that the limb deformations mentioned (club and bent foot) occur from abnormal bending of a long bone of the limb, a part of the limb separate from the phalanges, and that these limb deformations are not necessarily biologically related to delayed ossification of the phalanges (C. Lau, personal communication).

COMMENT: *Lau et al. (2006) indicated that the delay in ossification was not a simple developmental delay because it was present at birth and in the absence of a body weight effect.*

RESPONSE: As is the case for delayed ossification in Lau et al. (2006), delayed mammary gland development from developmental exposures also occurred at doses that do not cause decreased body weight or other effects, including increased liver weight which is well-established as a sensitive effect of PFOA. The fact that delayed ossification occurred in the absence of a body weight effect does not indicate that it has permanent functional consequences.

COMMENT: *Lau et al. (2006) stated that delayed puberty occurred in the absence of effects on body weight and was indicative of an effect on development.*

RESPONSE: This comment is incorrect in several ways. The endpoint used as the basis for the USEPA Health Advisory Reference Dose is **accelerated puberty in males**, not delayed puberty as stated in USEPA's comment. Also, Lau et al. (2006) did not state that the accelerated puberty effect used by USEPA as the basis for its Reference Dose occurred in the absence of body weight effects. In contrast, Lau et al. (2006) states: "It is noteworthy that this accelerated pubertal maturation took place despite a body weight deficit of 25–30%."

Again, these same considerations regarding functional significance of accelerated puberty are also true for delayed mammary gland development. The functional significance of accelerated puberty is not clear.

COMMENT: *The DWQI review of the USEPA Health Advisory indicates that another study (Yahia et al., 2010) in a different strain of rat* [NOTE: Both studies were in mice, not rats, as was stated in the comment] *indicates strain differences in sensitivity for the ossification effect. The report of delayed ossification in a different strain [of the same species] supports EPA's selection of delayed ossification from Lau et al. (2006) study as the critical effect rather than simply a manifestation of strain differences. In Yahia et al. (2010), delayed ossification occurred at higher doses than in Lau et al. (2006) and only occurred at doses that caused reduced body weight and postnatal mortality during the first four days of life. Although NJ DWQI concluded that Yahia et al. (2010) did not support the delayed ossification effects at 1*

mg/kg/day reported by Lau et al. (2006), EPA notes differences in reporting of this endpoint between Lau et al. (2006) and Yahia et al. (2010).

RESPONSE: As above, the point of these DWQI comments on the USEPA Health Advisory is not to dismiss delayed ossification as a valid endpoint, but to note that the reasons provided by USEPA to dismiss delayed mammary gland development for use in risk assessment do not appear to be valid and also apply equally to delayed ossification.

The data presented by Yahia et al. (2010) clearly show the ICR mice used by Yahia et al. (2010) are less sensitive to delayed ossification than the CD-1 mice used by Lau et al. (2006). In the comment above, acknowledges these strain differences, but states that the observation of delayed ossification in a second strain of mice supports the use of this effect from Lau et al. (2006) as the basis for risk assessment.

However, in regard to delayed mammary gland development, USEPA (2016a) mentions differences in strain sensitivity as a reason for uncertainty about the use of this effect. The USEPA Health Advisory (2016a) states that "*Tucker et al. (2015) found that CD-1 mice* [the strain used in most PFOA mammary gland studies, including Macon et al. (2011) used as the basis for the DWQI BMD modeling] *were considerably more sensitive to effects on mammary gland development (LOAEL 0.01 mg/kg/day) than C57BL/6 mice (NOAEL 0.1 mg/kg/day).*" However, close review of the data from Tucker et al. (2015) shows that C57/BL/6 mice actually are not less sensitive than CD-1 mice. As shown in the graphs of mammary gland development score vs. serum PFOA level data from Tucker et al. (2015) (Figure 1, below), C57Bl/6 strain is, if anything, more sensitive to delayed mammary gland development than the CD-1 strain. The lack of statistical significance at lower doses in the C57Bl/6 strain reported by Tucker et al. (2015) results from the larger standard deviation in this strain, likely due to the smaller number of mice per group at these doses (n=2-10) than for CD-1 mice (n=8-22).

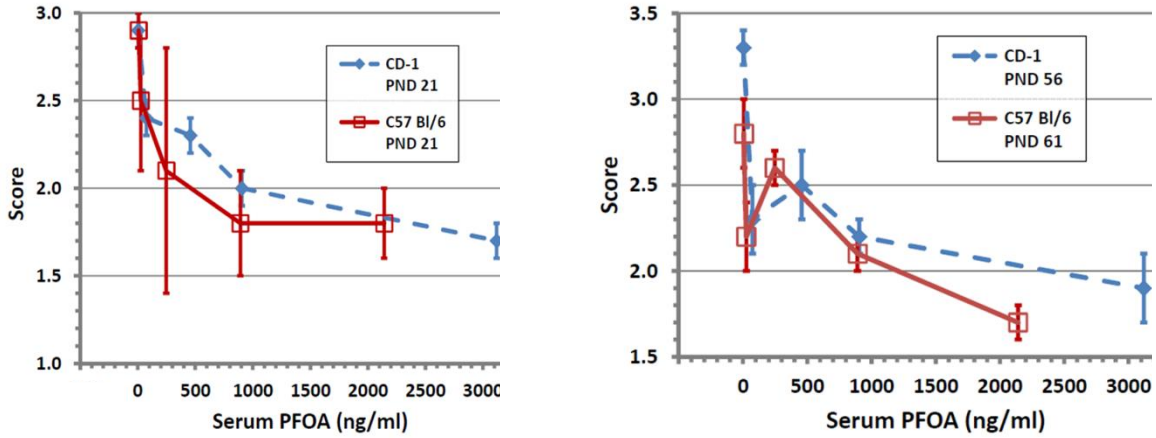

Figure 1. Serum PFOA concentration on PND 21 (Table 1 of Tucker et al., 2014) versus mammary gland developmental score on postnatal day 21 (PND 21) and PND 56 /PND 61 (Table 5 of Tucker et al., 2014). PND 21 serum PFOA data were used because this is the earliest time point at which serum PFOA was measured. Therefore, it represents the data closest to the end of the dosing period (gestation days 1-17) and the highest exposures for which data are available. Mammary gland development was scored from 1-4 based on "criteria including, but not limited to, lateral and longitudinal epithelial growth, branching density, changes in epithelial growth, appearance of budding from ductal tree, number of differentiating duct ends, and the presence or absence of terminal end buds (Tucker et al., 2014)."

COMMENT: *NJ DWQI states that the endpoints used as the basis for the USEPA Reference Dose (delayed ossification and accelerated puberty in Lau et al. (2006) do not follow a typical monotonic dose response curve in which greater effects occur with increasing external dose and are not appropriate for dose-response analysis based simply on a NOAEL or LOAEL. USEPA responds in its comments to the DWQI by stating that USEPA used a pharmacokinetic model to predict serum PFOA values from animal studies to be used as points of departure from animal studies, and that modeled human serum PFOA levels were converted to human equivalent doses (HEDs) by use of the clearance factor.*

RESPONSE: This comment is not relevant to the stated topic. The statement from the draft Health-based MCL Support Document (Appendix 2, p. 11) cited in this comment refers to the shape of the dose-response curves for the two endpoints used as the basis for the USEPA risk assessment. However, this comment is listed by USEPA under a heading ("Interspecies Conversion in RfD Development") that is not relevant to the shape of the dose-response curve. This comment does not address the statement about the shape of the dose-response curve cited from Appendix 2, but rather discusses the pharmacokinetic model used by USEPA for interspecies extrapolation, which is not relevant to this issue.

For both endpoints selected by USEPA, the dose-response curves do not show a greater effect with increasing dose, as shown in the graphs on p. 11 of Appendix 2 of the draft Health-based MCL Support Document. USEPA's response did not address DWQI's discussion of the non-monotonic nature of the dose-response curves or issues with extrapolation from the LOAEL to

the NOAEL when dose-response is non-monotonic. The LOAEL-to-NOAEL uncertainty factor is intended to extrapolate from the lowest dose at which an adverse effect occurs to a dose where no adverse effect is expected, and its application is based on the assumption that there is a greater effect as dose increases. For dose-response curves in which the effect does not increase with dose, the basis for application of this uncertainty factor is unclear and subject to debate.

5. Animal-to-human extrapolation in USEPA Health Advisory cancer risk assessment

COMMENT: *The DWQI document stated that USEPA's calculation of the cancer risk assessment did not consider the longer half-life in humans than rats. In its cancer risk assessment, USEPA used the standard interspecies adjustment based on body weight to the ¾ power, while DWQI applied a 120-fold uncertainty factor to account for the difference between a half-life in humans (2.3 years) and rats (7 days). USEPA comments that half-life should only be considered as a tool to adjust for species differences as it relates to the lifespan. Based the half-life to lifespan ratio for an interspecies adjustment, for the rats the ratio of half- life to life span is 0.01 (7 days ÷ 730 days (2 years) = 0.01). For a human the ratio is (2.3 years ÷ 70 years) = 0.03. The human ratio is 3 times greater than the animal ratio (0.03 ÷ 0.01 = 3). The body weight adjustment made by USEPA has the same impact as would an adjustment based on the human versus rat half-life to lifespan ratio of 3. Both would lead to an approximately 3-fold reduction in risk. Thus, the USEPA adjustment adequately reflects an adjustment for the rat to human differences.*

RESPONSE: The Health Effects Subcommittee definitively concludes that the much higher internal dose in humans versus animals from the same administered dose of PFOA must be accounted for, regardless of whether a cancer or a non-cancer endpoint is being evaluated. The ratio of human-to-rat half-lives of 120 applied by DWQI is not an "uncertainty factor" (as stated by USEPA) but is rather a data-based adjustment to account for interspecies differences in internal dose from the same administered dose. USEPA considered interspecies internal dose differences in its non-cancer risk assessment, and the lack of consideration of interspecies internal dose differences in the USEPA cancer risk assessment is inconsistent within its own document. The default approach used by USEPA (body weight to the ¾ power) and the explanation provided by USEPA regarding "half-life to lifespan ratios" in the comment above do not account for these interspecies internal dose differences**.** Use of internal dose, rather than administered dose, reduces the uncertainty in the risk assessment. This is especially important for a chemical such as PFOA for which the half-life is much longer in humans that experimental animals, resulting in much higher serum levels in humans than in animals from the same administered dose.

6. Consideration of human epidemiological data in USEPA Health Advisory

COMMENT: *USEPA stated that NJ DWQI rejects some of the reasons that USEPA used to support not using the epidemiology data in a quantitative manner (i.e. to derive the RfD). USEPA stated that reasons for not using the epidemiology data quantitatively include the potential for reverse causality related to effects on rates of PFOA excretion; lack of information on dose or exposure duration as related to appearance of the effect; factors such as diet, body weight, and genetics that may not have been controlled for and could affect endpoints such as cholesterol; and inability to separate out the effects of other PFAS that co-occur with PFOA and also show associations with health endpoints.*

RESPONSE: USEPA is not correct in stating that the Health Effects Subcommittee suggested that human epidemiology data be used as the basis for the Reference Dose. As stated on p. 12 of Appendix 2 of the draft Health-based MCL Support Document: "The Health Effects Subcommittee agrees that the human data have limitations that preclude their use as the primary basis for risk assessment [i.e. basis of RfD], but it does not agree with USEPA that the serum PFOA concentrations and PFOA exposures associated with human health effects are highly uncertain or unknown."

Accordingly, the DWQI is in general agreement with the USEPA Health Advisory statements that "the human data demonstrate an association between PFOA exposure and endpoints, including effects on serum lipids, antibody responses, fetal growth and development, and the liver. … The associations observed for serum lipids, and reproductive parameters and immunotoxicity are the strongest. …. Although the human studies collectively support the conclusion that PFOA exposure is a hazard, EPA concluded that, based on several uncertainties associated with the database, the human studies are adequate for use qualitatively in the identification hazard at this time."

However, the Health Effects Subcommittee concludes that the general ranges of serum levels associated with health endpoints in different study populations are well established (e.g. within the general population; within the elevated serum level range resulting from exposure to contaminated drinking water; higher exposure ranges from occupation exposure), while USEPA does not acknowledge that the serum levels associated with health effects are known. As discussed in the related comment below, ongoing exposure to drinking water at the USEPA Health Advisory of 70 ng/L by adults is predicted to result in average serum PFOA levels of approximately 10 ng/ml with average drinking water consumption, and about 16 ng/ml with upper percentile consumption. Serum PFOA levels associated in infants (breast-fed or formula fed) associated with 70 ng/L in drinking water are expected to be much higher than in older individuals. Clearly, consumption of 70 ng/L in drinking water will elevate serum levels to well above the general population range. This is of concern because associations with multiple health endpoints are observed within the general population

exposure range.

7. **Prediction of increase in human PFOA serum level from exposure to PFOA in drinking water**

COMMENT: *NJ DWQI states that USEPA does not acknowledge that increases in serum PFOA levels expected from exposure to 70 ng/L can easily be predicted. DWQI concludes that prediction of human serum levels from drinking water concentrations is technically sound and not subject to debate. NJ DWQI also stated that EPA does not acknowledge that multiple human health effects are consistently associated with serum levels below those expected from exposure to 70 ng/L in drinking water. USEPA responds to these DWQI points by stating that the clearance factor cannot be used for exposures resulting from drinking water guideline values such as 14 ng/L or 70 ng/L, because the clearance factor can only be used in the higher ranges of serum levels from animal studies that are used to determine points of departure in the USEPA model. USEPA states that exposure to drinking water at the Lifetime Health Advisory value of 70 ng/L is predicted to maintain a steady state level of PFOA/PFOS in serum that will not result in adverse effects in the general population.*

RESPONSE: A clearance factor that relates human PFOA exposures to human PFOA serum levels was developed by USEPA scientists (Lorber and Egeghy, 2011). This factor was developed to evaluate the levels of exposure and serum levels prevalent in the general population, including increases in serum PFOA from drinking water exposures. As discussed in the USEPA comment above, USEPA (2016a) used this same clearance factor to convert NOAEL and LOAEL serum levels from laboratory animals to human equivalent doses (p. 4-13 of USEPA, 2016a). The USEPA Health Effects Support Document (USEPA, 2016b) also discusses that the clearance factor relates human PFOA dose to human PFOA serum level, including from drinking water exposure (p. 2-51 of USEPA, 2016b).

The Health Effects Subcommittee concludes that the use of the clearance factor to predict increases in serum PFOA levels from drinking water exposures is technically sound and appropriate for the drinking water levels being discussed herein (e.g. 14 ng/L; 70 ng/L). Additionally, the Health Effects Subcommittee notes that Dr. Scott Bartell has developed a calculator (posted at http://www.ics.uci.edu/~sbartell/pfoacalc.html) that predicts the steady-state serum PFOA concentration that will result from exposure to a given concentration of PFOA in drinking water. The calculator also displays a graph of the increase in PFOA serum levels over time until steady-state is reached. Dr. Bartell is a professor at University of California Irvine who has published several studies related to modeling of PFOA serum levels in communities exposed through drinking water. The calculator uses a serum:drinking water PFOA ratio of 114:1, based on the mean ratio observed in the study of private wells in the C8 area by Hoffman et al. (2011) that Dr. Bartell co-authored. This ratio is identical to the ratio calculated from the clearance factor and mean U.S. drinking water consumption on p. 57 of the draft Health-based MCL Support

Document. The calculator's predictions of the serum PFOA levels at steady state from a certain drinking water level are also identical to those presented on p. 58 and p. 59 of the draft Health-based MCL Support Document. However, in spite of the very clear-cut nature of this issue, USEPA does not acknowledge that it is possible to predict the increase in serum PFOA that will result from ongoing exposure to a given concentration of PFOA in drinking water

Ongoing exposure to drinking water at the USEPA Health Advisory of 70 ng/L by adults is predicted to result in serum PFOA levels of about 10 ng/ml with average drinking water consumption, and 16 ng/ml with upper percentile consumption, with much greater serum PFOA levels in infants. As discussed in the draft Health-based MCL Support Document (e.g. p. 203-204; p. 220), several health effects, some with evidence satisfying multiple criteria for causality, are associated with PFOA exposures at serum levels well below those that would result from exposure to 70 ng/L (the USEPA Health Advisory) in drinking water. The Health Effects Subcommittee therefore concludes that elevations in serum PFOA levels of the magnitude expected from ongoing exposure to 70 ng/L in drinking water are not desirable and may not be protective of public health.

8. Inclusion of women who plan to become pregnant as sensitive subpopulation

COMMENT: *NJ DWQI states that USEPA developed a lifetime Health Advisory for the general population (adults ages 21 and older) of 100 ng/L and that USEPA indicated that this value is protective for effects other than developmental toxicity. NJ DWQI also commented that EPA states that sensitive subpopulations are pregnant and lactating women, and bottle-fed infants, but does not include women who plan to become pregnant.*

USEPA's Health Advisory for PFOA is 70 ng/L, based on the 90th percentile drinking water ingestion rate of lactating women, and this is the only Health Advisory recommendation provided. Both pregnant and lactating women are potentially more susceptible to health effects of PFOA than other adults, and the drinking water ingestion rate of lactating women is protective because it is higher than for pregnant women or other adults. As a comparative analysis, USEPA calculated a lifetime HA value for alternative exposure scenarios for the general population (adults ages 21 and older) of 100 ng/L.

RESPONSE: The statements on p. 7 of Appendix 2 of the draft Health-based MCL Support Document about the lifetime Health Advisory value based on the alternative exposure scenario for the general population have been clarified to be consistent with the language used by USEPA. The Health Effects Subcommittee agrees with USEPA that lactating women have higher drinking water exposures than other adults. However, it is not clear that a Health Advisory using higher exposures of lactating women is applicable to an RfD based on a steady-state serum level that is reached over a period of many years, since the higher ingestion during lactation occurs for a time much shorter than needed to reach

steady-state.

More importantly, the Health Effects Subcommittee concludes that women of childbearing age should be included in the groups defined as sensitive subpopulations, along with pregnant women and lactating women (p. 8 and p. 14 of Appendix 2). This is because serum PFOA levels that are elevated when a woman becomes pregnant will remain elevated throughout pregnancy and lactation due to the human long half-life of PFOA. **Therefore, exposures to PFOA in women of childbearing age prior to pregnancy pose a risk to the fetus and nursing infant. A sentence that clarifies this point has been added to Appendix 2 of the Health-based MCL Support Document.**