APPENDIX D

RESPONSES TO COMMENTS ON DWQI HEALTH EFFECTS SUBCOMMITTEE REPORT: "PUBLIC REVIEW DRAFT - HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT: PERFLUOROOCTANE SULFONATE (PFOS)"

May 25, 2018

Please Note:

- ***As the Drinking Water Quality Institute (DWQI) serves as an advisory body which makes recommendations to the New Jersey 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.***

- ***In some cases, comments are grouped together and one response is provided for several comments.***

- ***Page numbers mentioned in the responses refer to the <u>numbered</u> pages in the draft*** (http://www.nj.gov/dep/watersupply/pdf/dwqi-pfos-mcl-draft.pdf) ***linked here.***

Six submissions with comments relevant to the draft Health-based Maximum Contaminant Level (MCL) Support Document were received.

- American Chemistry Council submitted a letter (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-7.pdf

- Chemistry Council of New Jersey submitted a letter outlining comments specific to the Health Effects Subcommittee (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-3a.pdf) with three attachments:
    - Additional comments on the Health Effects Subcommittee Report (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-3c.pdf)
    - "Rutgers Pilot Study of Perfluorochemical Compounds in Paulsboro Residents: Preliminary Study Report" (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-3b.pdf)

  - "Adult Questionnaire" from the Rutgers Pilot Study (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-3d.pdf).
- Delaware Riverkeeper Network submitted a technical analysis prepared by Cambridge Environmental Consulting (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-4b.pdf).

- Alan Ducatman, MD, MS, Professor of Public Health and Professor of Medicine at West Virginia University, submitted a letter (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-5.pdf).

- Environmental Working Group submitted a letter (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-8.pdf).

- 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 (http://www.nj.gov/dep/watersupply/pdf/pfos-comment-6.pdf).

The Chemistry Council of New Jersey and the American Chemistry Council do not support the Health-based MCL recommendation and recommend consideration of the higher PFOS drinking water values from the USEPA (2016) Health Advisory and the draft Health Canada (2016) assessment. Comments from the Delaware Riverkeeper Network and the technical report submitted on their behalf, Dr. Philippe Grandjean, and the Environmental Working Group state that the Health-based MCL is not stringent enough to protect human health. Dr. Alan Ducatman expressed general support for the Health-based MCL.

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/or recently identified by the Health Effects Subcommittee. Additionally, minor edits were made 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

COMMENT: *NJDWQI's evaluation of animal and epidemiologic PFOS toxicity studies was comprehensive and rigorous. The New Jersey Department of Environmental Protection has been progressive in efforts to protect public health from PFOS, PFOA, and other perfluorochemical exposures. We concur with the process used to derive a PFOS reference dose, concluding with the Dong et al (2009) study showing an immunotoxic effect in test animals.*" (Delaware Riverkeeper Network)

COMMENT: *The State of New Jersey and its scientists from the Drinking Water Quality Institute are to be congratulated for a thorough, factual, defensible document, entitled Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). I am a clinician researcher, and I have contributed to the literature regarding PFOS and related products.*

There is little doubt of many documented health endpoints following exposure, including the immune system alterations following exposure in animals, which was used in the document as the most sensitive endpoint. In addition, there are important and parallel findings in human populations following exposure to the perfluoroalkyl substances such as PFOS. This means that we need to pay particular attention to the recommendation (Alan Ducatman).

COMMENT: *As with previous New Jersey efforts such as its parallel and preceding PFOA document, this is now the most thorough and up-to-date review available. As occurred following the publication and acceptance of the New Jersey PFOA document, other entities will adapt information from this document. Standard setting will trend towards the New Jersey level.* (Alan Ducatman)

COMMENT: *I support this standard because it is science-based, feasible to implement, and protective of the development of affected communities and persons living in them.* (Alan Ducatman)

COMMENT: *With this comment letter that we respectfully submit to the New Jersey Drinking Water Quality Institute, EWG strongly supports the overall approach taken by the state for setting the most stringent MCL for PFOS in the United States, and we urge the adoption of a more health-protective water concentration.* (Environmental Working Group)

COMMENT: *EWG thanks the DWQI for completing a scientific review of PFOS health impacts and proposing an MCL, as well as for its similar efforts with regards to PFOA and PFNA.* (Environmental Working Group)

COMMENT: *The health effects report provides important guidance and research analysis that can be utilized by regulatory agencies across the country and the globe. In the absence of federal leadership, it is encouraging that the state of New Jersey is moving forward to set a drinking water limit for PFOS contamination. The recent nationwide water testing required by the EPA identified PFOS as a ubiquitous contaminant in drinking water in New Jersey and across the country. In 2016 the EPA set a health advisory limit of 70ng/L for the combined concentration of PFOS and PFOA in drinking water, but has provided no indication that a national MCL will be established.* (Environmental Working Group)

COMMENT: *The DWQI Report summarizes the major adverse effects that have been documented in laboratory animals and also reported in humans. The effects include carcinogenicity, liver function abnormalities and elevated serum lipids, immunotoxicity, endocrine disruption (including delayed breast development), and reproductive toxicity. In the below text, I refer only to publications that are of particular relevance or not cited by the Report* (Philippe Grandjean)

RESPONSE: These supportive comments are acknowledged.

COMMENT: *The important scientific questions will be about whether the implicated Maximum Contaminant Level (MCL) is too high, and therefore permits ongoing risk to the human population. Based on the data presented, as well as on the need to set the standard at a level for which accredited laboratories can reproducibly and reliably report small differences in contamination levels, the proposed MCL has my full support.* (Alan Ducatman)

RESPONSE: This supportive comment is acknowledged. As mentioned in the comment, other commenters stated that the Health-based MCL is not sufficiently stringent. These comments are addressed below.

2. Consideration of additional PFOS evaluations

COMMENT: *ACC urges the Subcommittee to revise its health-based MCL to reflect a value that is appropriately supported by the available animal and human data and that is consistent with the analysis conducted by other authoritative bodies."* (American Chemistry Council)

COMMENTS:

- *We believe that it is in the best interests of public policy and public health in New Jersey to review this science prior to any final PFOS MCL recommendation from*

DWQI. These resources will provide valuable insight to DWQI and allow for the review of the best information currently available.

- *DWQI must be mindful of the science being developed in other states and by the federal government. The works completed by other states/countries and USEPA are also informative to DWQI's PFOS review. It is imperative that the Institute review these works, as they clearly help identify the flaws in New Jersey's current scientific literature regarding PFOS.*

- *Based upon available science and data, as further detailed below, we have significant concerns that DWQI's current recommendations related to PFOS are not justified, could not be feasibly implemented by New Jersey water providers, and is not supported by an objective analysis of the available science and data. As such, CCNJ/SRIN strongly recommend that DWQI's current draft Maximum Contaminant Level (MCL) for PFOS be held until such time that scientific evidence can support its recommendation. In the alternative, we urge DWQI to further review the detailed scientific data and literature that was either ignored or missed in its current review of PFOS before submitting a recommendation to the New Jersey Department of Environmental Protection (NJDEP); the following are specific examples:* [examples provided are below] (Chemistry Council of NJ)

RESPONSE: More scientific information related to health effects is available for PFOS than for most other environmental contaminants. The DWQI, including the Health Effects Subcommittee, has thoroughly and objectively evaluated the relevant scientific information on PFOS. As discussed in the draft Health-based MCL Support Document and shown in Appendix 1, an initial search for literature published through the end of 2014 yielded more than 2800 citations. This initial literature search was updated with additional monthly literature searches during development of the document. Additionally, the DWQI posted a request for submission of additional technical information in May 2014, and the information received in response to the request was considered by the Health Effects Subcommittee. Finally, as discussed below, the Subcommittee has recently become aware of several additional studies that provide further support for the recommended Health-based MCL. A review of these studies has been added to the Health-based MCL Support Document.

COMMENT: *The following are the specific examples provided by the Chemistry Council of NJ:*

- *Rutgers Environmental Health and Occupational Health Sciences Institute and School of Public Health. 2017. Rutgers Pilot Study of Perfluorochemical Compounds in Paulsboro*

Residents, Preliminary Study Report. September 13. … The Rutgers report is further discussed below.

RESPONSE: The Health Effects Subcommittee has reviewed this report. The commenter submitted additional detailed comments regarding this report. These comments and the responses are found in "Comments on 'Rutgers Pilot Study of Perfluorochemical Compounds in Paulsboro Residents, Preliminary Study Report' " below.

- *enHealth. 2016. Statement: Interim national guidance on human health reference values for per- and poly-fluoroalkyl substances for use in site investigations in Australia. June. http://www.health.nsw.gov.au/environment/factsheets/Documents/pfas-interimhealth-values-ahppc.pdf*

RESPONSE: The PFOS guidance cited by the commenter is out of date. On April 3, 2017, the Australian government released a review by Food Standards Australia New Zealand (FSANZ), "Perfluorinated Chemicals in Food" that lowered the Tolerable Daily Intake (TDI) and Drinking Water Quality Guidance for PFOS from the earlier values in document cited by the commenter (enHealth, 2016). FSANZ (2017) recommended a TDI of 20 ng/kg/day and a Drinking Water Quality Guideline of 70 ng/L for PFOS (CRC Care, 2018; https://www.crccare.com/knowledge-sharing/pfos-and-pfoa-guidelines). These values are lower than the earlier enHealth (2016) TDI of 150 ng/kg/day and Drinking Water Quality Guideline of 500 ng/L.

It is also noted that enHealth (2016) considered a number of existing risk-based values for PFOS developed by authorities in several nations and chose to use the European Food Safety Authority (EFSA; 2008) Tolerable Daily Intake (TDI) of 150 ng/kg/day. DWQI members have previously evaluated the basis for the EFSA (2008) TDI and concluded that it is not scientifically supportable or health protective. The EFSA TDI is based on a subchronic study with Cynomolgus monkeys (Seacat, 2002) and does not consider the numerous more recent human and animal studies reviewed by the Health Effects Subcommittee. In recognition that the current TDI is not up to date, EFSA is currently reviewing and updating its TDI for PFOS (http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2015-00526).

Importantly, the EFSA 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, it is generally accepted that the much higher internal dose from the

same administered PFOS dose in humans compared to animals should be quantitatively considered by basing the interspecies comparison on serum PFOA levels instead of administered dose.

In summary, the enHealth (2016) Drinking Water Quality Guideline of 500 ng/L is outdated and is not scientifically supportable, and it is unquestionably far higher than can be considered to be health-protective. Ongoing exposure to this drinking water level is predicted to result in serum PFOS levels of over 100 ng/ml, on average, far higher than the range associated with multiple health effects.

- *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*

RESPONSE: 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. 211 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 PFOS. 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.

3. The USEPA Health Advisory and the draft Health Canada Maximum Allowable Concentration in drinking water are higher than DWQI Health-based MCL

COMMENTS:

- *As discussed above and in Attachment 3, DWQI is proposing an MCL for New Jersey that is far lower than the guideline the federal government recently determined is protective for drinking water. No additional known health protection is achieved, suggesting the DWQI proposal does not overcome the additional cost and reporting/regulatory burden that would unnecessarily hinder economic growth and success in New Jersey.*

- *In situations where urgency is required and federal guidance is available, it is a sound policy for the State to rely on the federal guidance and allow the scientific process to develop data to support MCLs and other New Jersey environmental standards.*

- *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 PFOS in drinking water at the proposed Maximum Contaminant Level (MCL).*

- *USEPA has gathered a great deal of data, nationally, on PFOS and its potential health effects and, very recently, issued a federal protective guideline of 70 parts per trillion (ppt) for Perfluorooctanoic Acid (PFOA) + PFOS in drinking water. DWQI rejects the federal government's careful analysis and replaces it with its own approach which would lead to a far stricter guideline being imposed on the communities and businesses of New Jersey."* (Chemistry Council of NJ)

  COMMENT: *As the Committee notes, the US Environmental Protection Agency (USEPA) issued a health advisory (HA) of 0.07 micrograms per liter (µg/L) for PFOS in May 2016 under the federal Safe Drinking Water Act (SDWA). Earlier in 2016 the Federal-Provincial-Territorial Committee on Drinking Water within Health Canada proposed a maximum acceptable concentration (MAC) of 0.6 µg/L for PFOS in drinking water. Both of these guidelines were developed after a review of the available animal and human evidence. Yet, the Subcommittee's report dismisses these recommendations in lieu of a value based on inconsistent findings of immunotoxicity that have been thoroughly reviewed and rejected by both the US and Canada. In defending its proposal, the Subcommittee's primary rationale appears to be that "immune system toxicity is a more sensitive endpoint" than the effects used by USEPA and Health Canada. ACC is deeply concerned with the Subcommittee's disregard for US and Canadian guidance and the best available science and with its decision to base its proposal on the animal evidence that generates the lowest value while providing no substantive basis for asserting its significance to human health. We urge the Committee to withdraw its current proposal and to develop an MCL that is supported by the available evidence and consistent with the guidance provided by USEPA and Health Canada.* (American Chemistry Council)

  RESPONSE: The Health Effects Subcommittee has reviewed the USEPA PFOS Health Advisory and the draft Health Canada Maximum Allowable Concentration. 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. The Health Canada (2016) PFOS Maximum Allowable Concentration is a draft. It is subject to revision based on consideration of public comments and additional studies that have become available since it was developed. The

Health Canada assessment was mentioned in other comments and is discussed in more detail in responses to these comments below.

COMMENT: *It is neither sufficient, nor appropriate, for the Committee to recommend such a low MCL while admitting that it "does not understand the reasoning" behind specific criticisms of its approach offered by USEPA.* (American Chemistry Council)

RESPONSE: The phrase mentioned in the comment is from the following sentence on p. 325 of the draft Health Effects Support Document: "*The Health Effects Subcommittee does not understand the reasoning underlying this statement from USEPA*." The Health Effects Subcommittee did not intend to "admit" that it does not understand USEPA's reasoning, and the sentence will be reworded in the final document to prevent such misinterpretation by future readers. Furthermore, this statement is unrelated to the basis or derivation of the PFOS Health-based MCL. Rather, it refers to an earlier USEPA comment on the DWQI PFOA Health-based MCL Support Document about prediction of the relationship between PFOA drinking water levels and serum PFOA levels. See: http://www.nj.gov/dep/watersupply/pdf/comment5.pdf . The Health Effects Subcommittee presented a detailed response to the USEPA comment on pages 50-51 of "Responses to comments on DWQI Health Effects Subcommittee Report: 'Public Review Draft - Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA)' " at http://www.nj.gov/dep/watersupply/pdf/pfoa-appendixd.pdf . Some excerpts from the Subcommittee response are copied below:

> "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 uses a serum:drinking water PFOA ratio of 114:1.... 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."

4. Use of best available science

COMMENT: *Importantly, we support the use of the best available science; CCNJ/SRIN have always held this position. One recent example is the Site Remediation & Waste Management Program (SRWMP)'s revisions to Soil Remediation Standards (SRS). We submitted a letter of support to then-NJDEP Commissioner Bob Martin because we agreed that the latest USEPA Integrated Risk Information System (IRIS) toxicity values should be incorporated into NJDEP's calculations in determining revised SRS. CCNJ/SRIN stated our support of SRWMP's efforts because we support the use of the best available science, irrespective of whether the numbers ultimately increase or decrease.* (Chemistry Council of NJ)

RESPONSE: The Health Effects Subcommittee agrees with the commenter's support for use of the best available science and notes that the best available science was used to develop the Health-based MCL for PFOS. It also agrees that new scientific data may indicate the need to revise risk assessments for other chemicals that have been previously assessed to either a lower or a higher value.

SIGNIFICANCE OF PFOS ENVIRONMENTAL CONTAMINATION AND DRINKING WATER EXPOSURE

COMMENT: *As described by the DWQI Report, PFOS is a highly persistent chemical in the environment and has been disseminated globally. Known for many decades, PFOS is slightly water soluble and has a low vapor pressure, both of which are important properties that lead to environmental dissemination and retention in the human body.* (Philippe Grandjean)

COMMENT: *As the document points out, PFOS is detected in the serum of virtually all Americans. The levels of contamination were higher in the past; active intervention by Federal Agencies and cooperation from industry have resulted in decreased consumer-product exposure and documented decreases in serum PFOS concentrations in our nation, over time. This beneficial decline in internal contamination can be seen in the National Report on Human Exposure to Environmental Chemicals (Updated Tables, Vol 1, beginning on P 354, and publicly available at https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2017.pdf). Consumer-product exposure is the most common source, and the decrease in national consumer exposure is encouraging.*

However, as scientists from New Jersey have pointed out in the past, the improvement in serum PFAS contamination either does not extend to or is less applicable to those who suffer from ongoing exposure to contaminated drinking water. Once drinking-water contamination has occurred, it is understood to be long-lasting, requiring permanent

specialty treatment of water supplies, or acquisition of alternative water sources. Failure to replace or repair contaminated drinking water has important implications. When humans are continuously exposed to water contamination at some steady state level, the very long "half-life" in humans implies that internal bioconcentrations of the contaminant PFOS will not decrease in concert with the rest of the population, and can even continue to increase. The beneficial decrease seen in the rest of the population is less applicable or not applicable to those drinking contaminated water. Further, PFOS is passed transplacentally to developing humans, and in breast milk to newborns, so that mothers exposed to contaminated drinking water will pass on that contamination to their children. PFOS is not a chemical that can be safely ingested in drinking water. (Alan Ducatman)

RESPONSE: The Health Effects Subcommittee agrees with the commenters' points about exposure to PFOS from contaminated drinking water. Although production and use of PFOS in manufacturing has ended in the U.S., environmental contamination from previous manufacture and use will remain indefinitely, including in groundwater used for drinking water. As discussed in the Health-based MCL Support Document, continued exposure to PFOS in drinking water leads to elevated serum PFOS levels. Because PFOS is slowly excreted with a half-life of several years, body burdens remain elevated for many years after drinking water exposure ends. Exposure to the infant and fetus are of particular concern because PFOS causes developmental toxicity, and exposures to infants from contaminated drinking water are higher than in older individuals. Taken together, these considerations indicate the need for concern about exposure to PFOS from drinking water.

DEVELOPMENT OF REFERENCE DOSE (RfD)

1. Use of immune toxicity/decreased plaque forming cell response in mice as basis for RfD

COMMENT: *New Jersey has identified an immune system finding as it most sensitive endpoint. There are other systems affected, of course, the toxicity is not limited to the immune system. The most sensitive system does bear further discussion. The consequences of the immune system alterations following human exposure are not fully known, yet we known enough to be sure that there is unacceptable risk to exposed populations. For example, it has been shown that adolescents and adults exposed to PFOS mount a less robust immune response to vaccination when they have higher internal concentrations of PFOS. Exposure to PFOS has been associated with higher risk of important infectious diseases in young children, as well as with symptoms of infectious disease such as fever. Other findings of great concern in animal studies, such as the decreased ability to fight bacterial intestinal infections, have not been studied in living*

humans. If we continue to expose people, we will actually figure out how to do these studies, and we should not predict that we will like the results.

It is worth emphasizing that the New Jersey draft document makes important points that scientifically defensible and are so far not commonly found in parallel US Federal efforts. We can expect the New Jersey analysis to be emulated widely. One important point is the choice of the immune system changes as the current most sensitive endpoint. This will change only if still more sensitive endpoints are found (in which case, arguments for still lower thresholds will have additional merit).(Alan Ducatman)

RESPONSE: The Health Effects Subcommittee agrees with the commenter's support for use of immune system effects as the basis for the Reference Dose.

COMMENT: *I shall now focus on PFOS immunotoxicity, as this effect has been well documented and may well represent the critical adverse effect in humans, on which risk assessment should focus. PFOS-induced immune deficiency has been reported in mice, and increased mortality from virus infection has also been documented. In Rhesus monkeys, fairly crude outcomes, such as decreased spleen and thymus weights, lowered total immunoglobulin, and decreased leukocyte counts, were documented in an unpublished monkey study commissioned by a PFC producer 40 years ago. Based on the experimental and epidemiological evidence, the NTP recently concluded that PFOS must be "presumed to be an immune hazard to humans…," a conclusion that relied in part upon a "high level of evidence…from animal studies".* (Philippe Grandjean)

RESPONSE: The Health Effects Subcommittee is aware of the animal toxicology studies of effects of PFOS on the immune system that are summarized by the commenter. All of these studies are reviewed in the Health-based MCL Support Document with the exception of the older unpublished study of PFOS in Rhesus monkeys. The Support Document also discusses that, as mentioned by the commenter, the National Toxicology Program (2016) concluded from a thorough peer-reviewed systematic review of available human and animal studies that "PFOS is presumed to be an immune hazard to humans based on a high level of evidence that PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans."

COMMENT: *The Subcommittee's decision to focus on immune system effects as the basis for its proposed MCL runs directly counter to the specific concerns expressed about these data by both USEPA and Health Canada.* (American Chemistry Council)

COMMENT: *USEPA recognizes the lack of scientific evidence and uncertainties associated with the science related to any health effects associated with PFOS. In this regard, the choice of immunological effects as the critical effect is inconsistent with other*

regulatory agency review (USEPA; ATSDR; Australian Department of Health; Danish EPA) that have concluded that this endpoint requires further study before it can be considered human-relevant at the dose chosen as the Point of Departure (POD). Criticism of this endpoint from the other regulatory reviews included inconsistent immunosuppressive effects across studies in the database at this dose, questionable human relevance of the observations in mice, and unclear functional changes of in vitro effects at this dose suggesting that the findings may not represent an adverse effect. Further, epidemiological evidence in humans are inconclusive on the potential immunotoxicity of PFOS exposure, casting further doubt on the relevance of this endpoint to humans. (Chemistry Council of NJ)

RESPONSE: The Health Effects Subcommittee is aware of PFOS risk assessments developed by other agencies, including those cited by the commenters. In the risk assessments developed by various agencies, there is a general lack of consistency in the selection of the critical effect. Endpoints used as the basis for quantitative risk assessment by these organizations include decreased offspring body weight in rats (USEPA, 2016), hepatocellular hypertrophy in rats (Health Canada, 2016), and increased liver weight in monkeys (ATSDR, 2015).

It should be noted that the ATSDR (2015) evaluation of PFOS and other perfluoroalkyl acids is a draft that is subject to revision. 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 conclusions 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."

Additionally, the commenter fails to mention that another authoritative body, the National Toxicology Program (NTP; 2016), concluded from a thorough peer-reviewed systematic review of available human and animal studies that "PFOS *is presumed to be an immune hazard to humans"*, as discussed in more detail above. It is also noted that the evaluations cited by the commenter did not consider subsequent epidemiologic evidence (i.e. Dalsager et al., 2016; Goudarzi et al., 2017; Impinen et al. 2018) showing

statistically significant associations between gestational PFOS exposure and childhood infections.

Responses to each of the specific criticisms mentioned by the second commenter are provided below. It is noted that, while these points were attributed to the agencies mentioned by the commenter, the commenter did not provide specific citations to support their points and documents from the cited agencies that were review do not appear to contain the statements that the commenter mentions.

- *"inconsistent immunosuppressive effects across studies"*

  RESPONSE: The Health Effects Subcommittee does not agree with the characterization of immunosuppressive effects of PFOS as "inconsistent across studies". Only one of five PFOS studies that evaluated plaque forming cell response (PFCR) in mice was negative for this effect. Relevant to this point, the USEPA (2016) Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) notes a "…consistent suppression of SRBC response [i.e., PFCR] in animals…"

- *"questionable human relevance of the observations in mice"*

  RESPONSE: The Health Effects Subcommittee does not agree that the decreased PFCR observed in mice is of "questionable human relevance". PFCR in animals is an indication of antigen-specific IgM produced in response to a T-cell-dependent antigen (e.g. sheep red blood cells; SRBC). In humans, this antibody response is evaluated by measuring antigen-specific antibody levels following vaccination (i.e. a directly analogous antigen challenge). Relevant to this topic, it is noted that the Target Human Serum Level (analogous to Reference Dose, but in terms of serum level rather than administered dose) for PFOS based on Dong et al. (2009) is within the range of human serum PFOS levels that are statistically significantly associated with decreased vaccine antibody response.

- *"unclear functional changes of in vitro effects at this dose suggesting that the findings may not represent an adverse effect"*

  RESPONSE: It is not clear what is meant by "in vitro" since the PFCR assay is an indication of the *in vivo* immune system to response to an antigen. Furthermore, the Health Effects does not agree that the adversity of decreased PFCR is questionable. As discussed in the Health-based MCL Support Document (p. 256), USEPA IRIS agrees with this conclusion and has used decreased PFCR

as the basis for Reference Doses for at least two chemicals. This endpoint has also recently been identified as a sensitive toxicological endpoint that should be considered in risk assessment of PFOS by several other scientific groups. The Subcommittee concludes that such decreases represent an adverse effect, particularly since decreased PFCR is considered predictive of an immune-related health effect. Relevant to this point, PFOS has been associated with decreased antibody response to vaccination, and has been associated with the clinical effect of increased infection. We also note that Grandjean et al. (2012) found a statistically significant odds ratio for diphtheria and tetanus vaccine antibodies falling below the clinically protective standard as a function of PFOS concentration, providing further support for adversity of PFOS immune effects. Finally, the International Programme on Chemical Safety (IPCS, 2012) "Guidance for Immunotoxicity Risk Assessment for Chemicals" states, in reference to interpreting laboratory animal studies, that "any statistically significant effect should be considered meaningful, provided the quality of the animal data is sufficient." IPCS (2012) bases this conclusion on "the assumption that a linear relationship exists between loss of immune responsiveness and increased risk of developing disease [which is] consistent with our understanding of immunological processes and is supported by both laboratory animal … and human studies …. in which changes in immune tests correlated progressively with increased incidence of disease over a broad range." These statements from IPCS (2012) therefore supports the relevance of decreased PFCR as an appropriate endpoint for risk assessment. Additionally, consistent with the IPCS guidance, the Health Effects Subcommittee concludes that Dong et al (2009) is of sufficient quality to serve as the principal study for the derivation of a Health-based MCL.

- *"epidemiological evidence in humans are inconclusive on the potential immunotoxicity of PFOS exposure"*

RESPONSE: The Health Effects Subcommittee disagrees that the epidemiological evidence on immunotoxicity of PFOA is inconclusive. In contrast, the Subcommittee concludes that this evidence is generally consistent and supports a potential for PFOS to reduce vaccine response. As reviewed in the Health-based MCL Support Document and in the detailed response to comments on Human Epidemiology (below), all but one of five relevant epidemiology studies found an association between PFOS exposure and decreased antibody response to at least one vaccine. The only study that did not find an association (Looker et al., 2014) evaluated only influenza vaccine, and no association with this vaccine was found in the only other study in which it was evaluated (Granum et al., 2013). Although the data between infection and PFOS exposure is mixed,

four studies found positive associations which further support the immunotoxic potential of PFOS. Three of these four studies (Dalsager et al., 2016; Goudarzi et al., 2017; Impinen et al., 2018) were identified by the Health Effects Subcommittee after the draft Health-based MCL document was written and have been added to the final document.

COMMENT: *The Subcommittee offers little support for the relevance of the available animal and human data, which NTP is clear to caution may not be related to actual health effects in humans*. (American Chemistry Council)

RESPONSE: The Health Effects Subcommittee disagrees with this comment's characterization of the relevance of the animal and human data for immune effects of PFOS. NTP (2016) clearly states "The production, release, and increase in circulating levels of antigen-specific antibodies are important for protection against the infectious agent and preventing or reducing severity of influenza, respiratory infection, colds, and other diseases as part of the humoral immune response. Reduced antibody production is an indication of decreased immune function or immunosuppression that may indicate a greater risk of disease." NTP (2016) further states that "Antigen-specific IgM to a T-cell-dependent antigen (e.g., SRBC) is considered one of the most predictive measures of overall immune function because proper response requires cooperation between T-cells, B-cells, and antigen-presenting cells to develop an antibody response (Luster et al. 1992). This antibody response can be examined by measuring antigen-specific antibody levels after vaccination in humans and after challenge with SRBC or other antigens in laboratory animals."

COMMENT: *...Moreover, while asserting that the SRBC response in mice are "analogous" to decreased vaccine response in humans, the Committee offers no supporting information and neither USEPA nor Health Canada have reached a similar conclusion.* (American Chemistry Council)

RESPONSE: As we have stated above, plaque forming cell response in animals is a measure of antigen-specific IgM to a T-cell-dependent antigen (e.g., SRBCs). In humans, this antibody response is examined by measuring antigen-specific antibody levels following vaccination. As such, both endpoints indicate antigen-specific antibodies following antigen challenge. Therefore, these endpoints in animals and humans can be described as directly analogous. The USEPA and Health Canada assessments are addressed in the comments above.

COMMENT: *"The Subcommittee points to two 2017 publications as further evidence of the relevance of the immune system effects. Rather than provide any new data, these publications merely confirm that immune system toxicity is a more sensitive endpoint*

than the developmental effects on which USEPA based its HA. (American Chemistry Council)

RESPONSE: The two additional publications, Dong et al. (2017) and Lilienthal et al. (2017), demonstrate that other scientists concur with the Health Effects Subcommittee's conclusion that immune system effects are sensitive and relevant endpoints for PFOS toxicity. The Subcommittee agrees with the commenter that immune system toxicity is a more sensitive endpoint for PFOS than developmental effects such as decreased fetal growth.

2. Use of decreased plaque forming cell response (PFCR) from Dong et al. (2009) as key endpoint and study for Reference Dose development

COMMENT: *The 2016 NTP systematic review of the animal data concluded that it cannot be confident in the outcome assessment of the Dong 2009 study that the Subcommittee uses as a basis for the proposed MCL.* (American Chemistry Council)

RESPONSE: This comment misrepresents NTP's evaluation of outcome assessment of the Dong et al. (2009) study. NTP did not provide a definitive statement (e.g., "cannot be confident") regarding its confidence in the outcome assessment. As part of its risk of bias analysis of the studies that it evaluated, including Dong et al. (2009), NTP rated the risk of bias question "Can we be confident in the outcome assessment?" as "probably high risk of bias" based on either "indirect evidence of high risk-of-bias practices" or "insufficient information provided about relevant risk-of-bias practices." As noted by NTP, the Dong et al. (2009) study did not report whether outcome assessors were blinded to the exposure groups (as is the case for most toxicology studies published in peer-reviewed journals), and the study authors did not provide that information when contacted by NTP. Also as part of this question, the NTP noted that "well-established methods" were used to measure PFCR in this study. Based on consideration of a number of relevant factors, including evidence of dose-response across multiple studies, magnitude of the effect, consistency, potential for publication bias, and several others, NTP concluded that there is high confidence that exposure to PFOS is associated with suppression of the antibody response based on the available animal studies. The results show consistent suppression of the primary antibody response (PDF p 68).

COMMENT: *In the mouse study by Dong et al. (2009), NK cell activity was reported to increase at 0.083 mg/kg/day and to decrease at doses 10-fold higher (0.833 mg/kg/day) after 60 days.* (American Chemistry Council)

RESPONSE: The intent of the comments regarding the NK cell activity is unclear. The

Health Effects Subcommittee acknowledges the non-monotonic response of this endpoint. It is not related to the SRBC response and was not used as the basis for the MCL.

3. Dong et al. (2009) compared to other toxicological studies of immune effects

COMMENT: *Five studies have investigated potential effects on the immune system -- natural killer (NK) cell activity and sheep red blood cell (SRBC) response -- in mice exposed to PFOS. Although the studies reported immune effects, USEPA concluded that the differences in the levels at which effects were reported (and conflicts in the direction of the effects) "highlight the need for additional research to confirm the [no-observable-adverse-effect level or NOAEL] and [lowest-observable adverse-effect level or LOAEL] for the immunological endpoints." Health Canada reached a similar conclusion noting that "[f]urther exploration should be performed to address the nearly two orders of magnitude difference in LOAELs in the studies before these endpoints can be reliably considered as a basis for risk assessment." The inconsistency of these study results is detailed below.*

The 2008 study by Peden-Adams et al. (2008) identified decreased SRBC response in male B6C3F1 mice exposed to 0.0017 milligrams per kilogram per day (mg/kg/day) after 28 days of treatment, although no overt signs of toxicity were observed at doses up to 0.166 mg/kg/day. Additionally, the study observed enhanced NK cell activity at the lowest PFOS doses, but suppressed activity at higher doses.

In the study by Keil et al. also published in 2008, B6C3F1 mice exposed during gestation had decreased NK cell activity in males (at 1 mg/kg/day) and females (at 5 mg/kg/day) at postnatal week 8 – the opposite of the effect reported by Peden Adams. SRBC response was suppressed in males, but at doses several orders of magnitude higher (5 mg/kg/day) than in the study by PedenAdams. No SRBC response was reported in females.

A 2009 study by Zheng et al. reported decreased NK cell activity in male C56BL/6 mice exposed to 1 mg/kg/day over 7 days. Additionally, SRBC response was observed in males at 5 mg/kg/day – consistent with the report from Keil. (American Chemistry Council)

RESPONSE: The Health-based MCL Support Document discusses the differences in NOAELs and LOAELs between the animal studies assessing immunotoxicity, particularly plaque forming cell response, and notes that these differences may reflect methodological differences between studies (e.g., dose selection, strain, source of SRBCs). The study selected as the basis for the Health-based MCL was not the most or the least sensitive of the four studies showing that PFOS causes this effect, and was

selected for reasons discussed in the Health-based MCL Support Document. Additionally, the Health Effects Subcommittee concludes that the database for immunotoxicity of PFOS clearly demonstrates a consistent observation of decreased plaque forming cell response. This conclusion is supported by other recent assessments of PFOS. In its 2016 "Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)", the USEPA acknowledges "…the consistent suppression of SRBC response in animals." Additionally, the NTP (2016) systematic review concluded that there is "a high level of evidence that PFOS suppressed the antibody response from animal studies".

COMMENT:

- *In a subsequent [to Dong et al., 2009] study, Dong et al. (2011) observed no SRBC response at 0.0167 mg/kg/day.* (American Chemistry Council)

- *As described above, the results of the Subcommittee's key study conflict with those reported by other researchers and by a 2011 study conducted by the same research group.* (American Chemistry Council)

RESPONSE: These comments about differences in dose-response for SRBC response between Dong et al. (2009) and Dong et al (2011) are misleading. The two studies measured different endpoints following SRBC inoculation. In Dong et al. (2009), "SRBC response" was evaluated with the plaque forming cell assay, which is an assessment of immune function. In Dong et al. (2011), the "SRBC response" was assessed by measuring serum levels of IgM, which is an observational immune endpoint and does not address specific antibody function.

COMMENT: *It is key to be able to compare results of studies with the same endpoint and, preferably, the same route of administration. Dong et al., 2011 did not find effects on body, spleen, or thymus weight with oral gavage exposure for 60 days and evaluated functionality of the immune system by measuring antibody and assessed delayed hypersensitivity. The Dong et al., 2011 study serum NOAEL and LOAEL for immunotoxicity were 2,360 and 10,750 ng/l, respectively. This study was not considered in the final study selection for MCL derivation. However, an earlier study by Dong (Dong et al., 2009) was selected in this evaluation for effects on the immune system (decreased plaque forming immune response) as well as liver weight increase (no histology conducted).* (Chemistry Council of New Jersey)

RESPONSE: This comment contains factual errors. Contrary to the statements in the comment, effects on body, spleen, and thymus weights were observed from an administered PFOS dose of 0.83 mg/kg/day in Dong et al. (2011). However, a decrease in serum IgM levels was indeed observed with a LOAEL of 10,750 ng/ml (erroneously

stated as "10,750 ng/l" in the comment), and no effect was observed for hypersensitivity as indicated by footpad thickness. The footpad assay is not comparable in design to the PFCR assay. Additionally, as conducted in this study, it measures a different antibody response, IgG, than the PFCR assay which measures IgM. The footpad assay from Dong et al. (2011) was not considered for use in deriving the Health-based MCL derivation because the serum level LOAEL for the most sensitive endpoint in this study (decreased serum IgM levels) was >10,000 ng/ml, the cutoff used for identifying sensitive non-cancer endpoints for dose-response analysis. Additionally, decreased total serum IgM level is considered to be less predictive of immunotoxicity, and therefore less biologically significant, than the decreased PFCR reported in Dong et al. (2009).

4. Immune suppression as secondary to other toxicity

COMMENTS:

- *PFOS administration to laboratory animals, including mice and rats, can produce toxicity such as body weight loss and liver enlargement, as well as effects on the immune system. However, for many studies, it is unclear whether PFOS is directly immunotoxic or is a result of general toxicity and stress.* (Chemistry Council of NJ)

- *DWQI's selection of the direct toxicity (immune system) no observed adverse or lowest observed adverse effect levels (NOAEL and LOAEL, respectively) is questionable because of the presence of systemic toxicity (liver).* (Chemistry Council of NJ)

- *As reported in DWQI's document, PFOS exposure results result in suppression of adaptive immunity without toxicity; however, the administrated doses and serum concentrations at which these effects are produced vary widely.*
  The study selected as evidence of direct immunotoxicity (Dong et al., 2009) had signs of liver toxicity as well as immunotoxicity, while the more recent study did not. Dong et al., 2011 produced immunotoxicity without any other signs of toxicity that would confound the interpretation of direct immunotoxicity. The Dong et al., 2009 NOAEL is 3.5 lower than that from the Dong et al., 2011 study that effectively resulted in a lower PFOS MCL than would have been derived from the Dong et al., 2011 study. (Chemistry Council of NJ)

- *The selection of Dong et al., 2009 and the endpoint of immunomodulation (plaque forming cell assay results) is questionable as described above. Lefebvre et al., 2008 assessed the effects of PFOS on the immune system from dietary for 28 days at levels ranging from 2 to 100 mg/kg that are known to alter hepatic function. The authors concluded that "changes in immune parameters in rat did not manifest as functional alterations in response to immune challenge with KLH and may be secondary to hepatic-*

mediated effects of PFOS in this model" (Lefebvre et al., 2008). Therefore, for derivation of the MCL, hepatic endpoints would be the more sensitive endpoint and should have been considered rather than immune modulation since protection of the hepatic endpoint would likely be protective of immune modulation. It does not appear that this study was considered in DWQI's MCL evaluation. (Chemistry Council of NJ)

RESPONSE: The available evidence supports the conclusion that liver toxicity and decreased plaque forming cell response caused by PFOS are independent phenomena. In some studies, decreases in plaque forming cell response occurred in the absence of an effect on the liver (Keil et al., 2008; Peden-Adams et al., 2008). Conversely, liver toxicity occurred in the absence of an effect on plaque forming cell response in Qazi et al. (2010). In Dong et al. (2009), the LOAEL for decrease in plaque forming cell response coincided with a small (12%) increase in relative liver weight (histopathological examination was not performed). Based on the above, the Health Effects Subcommittee concludes that the assumption that immune suppression is secondary to hepatic toxicity is entirely speculative.

In regard to stress, serum corticosterone was increased at an administered dose 10 times greater than the LOAEL for decreased PFCR in Dong et al. (2009).

The Lefebvre et al. (2008) rat study is discussed in the Health-based MCL Support Document, and details are included in a table in Appendix 5. Because of the very large number of animal studies for PFOS, studies with less than 30 days of exposure such as Lefebvre et al. (2008) were considered as supporting studies but were not used for dose-response analysis in derivation of the Health-based MCL. Additionally, Lefebvre et al. (2008) is the only study of immunoglobulin levels and hypersensitivity in rats, and conclusions cannot be made about these effects in rats without additional studies. That being said, it is noted that a Health-based MCL based on the most sensitive hepatic endpoint in Lefebvre et al. (2008), increased relative liver weight in female rats, would be below 3 ng/L. This calculation is based on application of appropriate uncertainty factors (UFs) to the serum LOAEL for increased relative liver weight in female rats of 1.50 µg/g (~1500 ng/ml, based on the conversion of ng/g to ng/ml from Peden-Adams et al., 2008). A total UF of 300 is used (3 for interspecies toxicodynamic differences; 10 for intra-human variability; 10 for LOAEL-to- NOAEL) to arrive at a Target Human Serum Level of 5 ng/ml. (Note: A UF for less-than-chronic exposure was not applied, although the study is only 28 days long, since this UF was not used in the DWQI Health-based MCL for PFOA based on a short-term study of this same endpoint.) Based on the clearance factor and exposure factors used in the Health-based MCL Support Document, the resulting RfD and Health-based MCL are 0.4 ng/kg/day and 3 ng/L, respectively. This MCL is several-fold lower than the recommended Health-based MCL of 13 ng/L. This

lower Health-based MCL based on a different endpoint from a shorter duration study supports the conclusion that the recommended Health-based MCL of 13 ng/L is not overly stringent.

5. Relevance of exposure route (dietary versus gavage)

COMMENTS:

- *The implication of the difference in gavage (or bolus) and dietary dosing regimens is relevant to DWQI and the New Jersey Department of Environmental Protection (NJDEP) in the selection of POD, NOAELs and LOAELs, and, as such, the determination of the reference dose (RfD) used to develop the proposed health-based MCL.*

  In Table 38 of DWQI's PFOS Health Effects Subcommittee Report, the PODs, NOAELs, and LOAELs based on serum PFOS concentrations from four key studies are provided along with the target endpoint. This is reproduced below for illustration, with the addition of one column for route of administration/duration of exposure and two rows for additional studies (Dong et al., 2011 and Qazi et al., 2010 (2010a reference in the Draft MCL documentation)). While the POD for these two additional studies were not determined for purposes of this review, the NOAEL and LOAEL for immunotoxicity or immunomodulation is provided. These additions better inform the interpretation and selection of the key study for MCL derivation.

  In DWQI's MCL support document, the study used to derive the MCL was Dong et al., 2009. As can be gleaned from the table, this study was a 60-day oral gavage study, as were the rest of the key studies identified by the authors of this document except for the Butenhoff et al., 2012 study, which was chronic (up to 104 weeks) dietary administration up to 20 ppm PFOS. [Comment includes republished Table 38 of DWQI's PFOS Health Effects Subcommittee Report] (Chemistry Council of NJ)

- *It is well established that the route of administration has profound effects on the internal dose, e.g., serum concentrations, as demonstrated in various sources (Marty et al., 2007, Hayes 2007). Daily exposure by oral gavage results in bolus doses is inconsistent with dietary or drinking water exposures, lacking relevance to human exposures such as drinking water.* (Chemistry Council of NJ)

  RESPONSE: The Health Effects Subcommittee does not agree that gavage exposure over an extended period (e.g. 60 days, as in Dong et al., 2009) is not relevant to drinking water exposure for a compound such as PFOS that has a long half-life. Potential differences in absorption of PFOS due to dosing route are accounted for by the use of internal dose (serum PFOS level) as the dose metric. We recognize that for some contaminants with short half-lives,

greater toxicity may occur from the higher peak serum levels that result from bolus (e.g. gavage) dosing than from more continuous (e.g. dietary) dosing. However, for a daily bolus dose of a chemical with a long half-life, such as PFOS (40 days in male mice; Chang et al., 2012), the critical factor determining short term concentration at the target organ is the number of doses per half-life. In the case of the Dong et al. (2009) study, there were 40 doses during each PFOS half-life. From a basic toxicokinetic standpoint, this rate of dosing would result in insignificant short-term fluctuations in serum and target organ PFOS concentration. Furthermore, the average concentration over the course of the dosing period (AUC) will be essentially equivalent for gavage and dietary exposure over the 60-day dosing period in Dong et al. (2009).

Furthermore, in Dong et al. (2009), as well as Peden-Adams (2008), Zheng et al. (2009) and Keil et al. (2008), PFOS was delivered in aqueous solution. Therefore, as with drinking water exposure, there was no delay in absorption from the gastrointestinal tract as might occur with dietary exposure, where the physical and chemical properties of the food may impede absorption of contaminants. The gavage dosing in these studies was, therefore, more directly relevant to the determination of a drinking water Health-based MCL than the dietary dosing in Qazi et al. (2010). In addition, if exposure by gavage route did, in fact, cause greater toxicity than dietary exposure, a higher serum PFOS concentration would be expected from the same PFOS dose administered by gavage as compared to dietary exposure. The table below compares the ratio of administered PFOS dose to serum PFOS concentration at the LOAEL or NOAEL, approximately 24 hours after the last dose, in the PFCR studies. As shown, the ratio from Qazi et al. (2010a) is comparable to those from Dong et al. (2009) and Peden-Adams et al. (2008), and much less than the ratio from Zheng et al. (2009). This suggests that the kinetics of absorption and distribution, and thus the toxicity were not dependent on the route of exposure.

Study	**Route of Exposure**	**Administered PFOS dose:serum PFOS concentration at sacrifice (~ 24 hrs after last PFOS exposure) (mg/kg/d)/(ng/ml x 10^{-5})**
Dong et al. (2009)	gavage	1.1 (for LOAEL dose)
Peden-Adams et al. (2008)	gavage	1.9 (for LOAEL dose)
Zheng et al. (2009)	gavage	4.5 (for LOAEL dose)
Qazi et al. (2010a)	diet	2.1 (for NOAEL dose; only dose used)

Based on the above, the Health Effects Subcommittee concludes that studies using gavage exposure are appropriate as the basis for the Health-based MCL.

COMMENT: *In studying the difference in dosing regimens, Marty et al., 2007 reported that gavage administration resulted in an order of magnitude higher blood levels than the dietary route of exposure*. (Chemistry Council of NJ)

RESPONSE: Marty et al. (2007) cited by the commentator is not relevant to gavage versus dietary dosing for PFOS for several reasons. First, it is a study of chlorpyrifos and its metabolite in rats. In contrast to PFOS, for which the half-life in rats in about 40 to 67 days, the half-life of these compounds in rats is only several hours. Therefore, large intra-day fluctuations in blood levels occur with daily gavage dosing with chlorpyrifos. In contrast, as described above, daily gavage dosing with PFOS does not cause substantial fluctuations in serum PFOS levels. Additionally, Marty et al. (2007) did not compare chlorpyrifos blood levels from gavage versus dietary exposure in the same study. Marty et al. (2007) gave chlorpyrifos by gavage to lactating dams, and blood levels were estimated from levels in milk and the published milk:blood ratio. These estimated maternal blood levels were compared to data from an earlier study for peak and 24-hour average chlorpyrifos blood levels in lactating dams dosed by gavage. It is noted that the order of magnitude higher blood levels from gavage versus dietary exposure mentioned by the commenter is based on the peak blood level from gavage dosing, while the difference based on average blood levels, a more appropriate comparison, is only 3-fold.

COMMENT: *Instead of considering the route of administration (bolus versus dietary), DWQI chose not to use the dietary data because it resulted in less stringent doses than the bolus, which is a flawed assessment. As further support for this critical point, researchers opine that gavage administration should be abandoned for hazard assessments associated with endocrine disruptors like PFOS (Vandenberg et al. 2014).* (Chemistry Council of NJ)

RESPONSE: There are several fundamental problems with this comment.
First, PFOS is not a clear or primarily an endocrine disruptor. There is no evidence that immunosuppression as measured by PFCR involves the endocrine system. Additionally, the issues raised by Vandenberg et al. (2014) about gavage dosing in studies of endocrine disrupting chemicals are not relevant to PFOS and/or Dong et al. (2009). Toxicokinetics, including metabolism, of some compounds such as bisphenol A are different when absorbed through the oral mucosa versus the gastrointestinal tract, but this issue is not relevant to toxicokinetics of PFOS. It has been reported that stress caused by gavage dosing can influence the response of the endocrine system. However, Dong et al. (2009) measured serum corticosterone levels as a specific indicator of stress, and levels were only elevated at doses at least an order of magnitude greater than the LOAEL for decreased PFCR. It has also been reported that inexpert gavage administration can damage the esophagus. However, there is no information to suggest that this occurred in

any of the studies of PFOS and PFCR. Additionally, there is no evidence that this issue could affect the dose-related decrease in PFCR caused by PFOS.

COMMENT: *Referring to the liver toxicity endpoints in the table above, the NOAEL and LOAEL (a sensitive indicator of liver toxicity – microscopic liver cell hypertrophy) from the chronic dietary administration of PFOS are 2,554 and 11,724 ng/ml, respectively. This indicates that higher levels of PFOS are tolerated without affecting liver hypertrophy when compared to the oral gavage studies producing liver weight increases with NOAEL and LOAEL serum concentrations of 674 to 8,210 ng/ml, respectively. If Butenhoff et al., 2012 study's liver cell hypertrophy was selected as the MCL endpoint, a higher RfD by a factor of approximately 4 would have been developed compared to the less sensitive indicator of liver toxicity (liver weight increase) in the Dong et al., 2009 study. Higher RfD would result in a higher MCL. While the liver toxicity endpoint was not selected for the MCL, this demonstrates the dramatic differences in kinetics and exposure levels producing toxicity from 60-day gavage or bolus versus chronic dietary administration. This important difference was NOT considered in DWQI's document. As noted previously, oral gavage or bolus dosing is not consistent with humans exposed to concentrations in environmental media, including drinking water."* (Chemistry Council of NJ)

RESPONSE: As mentioned by the commenter, liver cell hypertrophy from Butenhoff et al. (2012) was not used as the basis for the RfD and health-based MCL because decreased plaque forming cell response was a more sensitive endpoint; it should be noted that Butenhoff et al. (2012) did not evaluate this endpoint. The NOAEL and LOAEL values for increased relative liver weight from gavage exposure to PFOS cited in the comment are from two different studies in mice. The NOAEL is from Dong et al. (2009) and the LOAEL is from Dong et al. (2012a). In contrast, the NOAEL and LOAEL for hepatocellular hypertrophy from dietary exposure (Butenhoff et al., 2012) cited in the comment are from a rat study. The difference in species is likely to be a far more important factor in accounting for differences in NOAELs and LOAELs than the route of exposure (gavage vs. dietary). Therefore, conclusions about the influence of route of exposure cannot be made from this comparison. Furthermore, among the PFCR studies, the ratio of administered dose to serum concentration from the dietary administration study (Qazi et al., 2010a) is comparable to the ratios from the gavage studies. These data support the conclusion that the route of exposure was not an important factor in the differing LOAEL and NOAEL values among these studies. Finally, as we have also noted in our responses, studies using gavage exposure are an appropriate basis for drinking water risk assessment of PFOS.

COMMENT: *As can be seen in [Table 38 of DWQI's PFOS Health Effects Subcommittee Report], dietary route of exposure does not produce adverse impacts on*

the immune system at much higher internal exposure levels compared to the Dong et al gavage studies. Previous studies by Qazi et al evaluated a wider range of exposure doses and concluded that, in contrast to gavage studies, dietary exposure to environmentally relevant doses does not compromise humoral immune response. This finding is supported by Lefebvre et al., 2008 (dietary study in male and female rats), where the authors found dietary exposure did not correspond to findings from oral gavage studies. (Chemistry Council of NJ)

RESPONSE: The commenter concludes that Lefebvre et al. (2008) did not find immunosuppression from PFOS exposure specifically because the route of exposure was dietary as opposed to gavage. However, this conclusion is not supportable, as there were several major differences between Lefebvre et al. (2008) and the studies showing immunosuppression (e.g., Dong et al., 2009) other than exposure route. First, as discussed above, Lefebvre et al. (2008) used rats while Dong et al. (2009) used mice. There is no *a priori* reason to assume that rats and mice would be equally sensitive to the immunosuppressive effects of PFOS. In general, the most sensitive endpoint and/or species is used as the basis for risk assessment, unless there are data indicating that the effect or species is not relevant to humans. Epidemiology studies that provide evidence of human immunosuppression from PFOS further support the use of the mouse immunosuppression data. Additionally, the antigen used in Lefebvre et al. (2008) (keyhole limpet hemocyanin, KLH) was different from the one used in Dong et al. (2009) (SRBC). As noted by Lefebvre et al. (2008): "This raises the possibility that choice of antigen may also contribute to apparent differences in the extent to which PFOS alters immune response." Finally, as discussed above, the assay used by Lefebvre et al. (foot pad swelling) was fundamentally different from the assay used by Dong et al. (PFCR) in both their designs and the antibodies measured. The footpad assay measures an IgG-specific response, while the PFCR assay measures an IgM-specific and antigen-specific response. As noted by Lefebvre et al. (2008): "A further possibility is that PFOS exerts a greater effect on primary IgM responses, as measured by the PFCR assay, than on the secondary IgG response, as measured after two immunizations with KLH." Given these very substantial differences between the two studies, there is no basis to conclude that the different routes of exposure account for the difference in results between Lefebvre et al. (2008) and Dong et al. (2009). It is unclear which studies by Qazi are being referred to by the commenter. We reviewed all studies of PFOS by Qazi that were identified, and data from these studies do not support the points made in the comment.

COMMENT: *As discussed above, nondietary studies produce liver effects at lower internal exposure levels (serum ng/l). This is supported from immunomodulation studies as well. Dietary exposure for 28 days in rats found no effects on immune tissue weight, cellularity, plaque forming cell assay, or cell activity (i.e. serum IgM and IgG (Qazi et*

al., Int Immunopharmacol. Nov;10(11):1420-7 (2010b reference in the Draft MCL documentation)). However, there was other evidence of toxicity (i.e. decrease in body weight gain and increase in liver weight). The NOAEL serum concentration for immunotoxicity was 11,600 ng/l but the NOAEL may be higher since this was the only dose studied. (Chemistry Council of NJ)

Apparently, Qazi et al., 2010 negative findings were dismissed from consideration in this evaluation because of positive findings in other studies evaluating plaque forming cells all using oral gavage (e.g. Dong et al., 2009 and 2011 (Table 44)). This negative finding was explained by "methodological difference" but the finding was dismissed rather than putting the results in context of bolus dosing. This process appears to be biased and not scientifically robust. (Chemistry Council of NJ)

RESPONSE: Qazi et al. (2010) was not "dismissed." The Health-based MCL Support Document includes a detailed discussion of possible reasons why this study did not find an effect of PFOS on PFCR, in contrast to the four studies showing that PFOS caused this effect. The commenter suggests that the route of exposure was the primary difference between the Qazi et al. (2010) and these other studies. However, other potentially significant differences were noted by the Health Effects Subcommittee, including that Qazi et al. (2010) used a different PFOS salt (tetraethylammonium) than the other four studies (potassium). Additionally, Qazi et al. (2010) used only one dose level, precluding evaluation of dose-response, while multiple doses were used in the other four studies. As discussed in the Health Effects Subcommittee document, and above, gavage dosing is an appropriate model for drinking water exposure to PFOS. Additionally, the dose:serum ratio of PFOS were similar for Qazi et al. (2010) and the gavage studies. While the reason for the difference in results from Qazi et al. study (2010) and the four positive PFCR studies remains unclear, the Health Effects Subcommittee concludes that the route of exposure is neither a relevant distinction, nor a likely cause of this difference. Therefore, the choice of a positive study, supported by three other positive studies as well as epidemiology data, is clearly more appropriate than the choice of the only negative study.

COMMENT: *Based on Table 42 of DWQI's PFOS Health Effects Subcommittee Report, and using Butenhoff et al., 2012 as the most sensitive noncancer endpoint (hepatocellular hypertrophy) for determination of MCL, the RfD of 12 ng/day was derived by the authors of the draft MCL document. The selection of endpoint and critical study alone would result in an approximately 7-fold higher MCL (i.e. 84 ppt versus 13 ppt). In conclusion, focusing on both factors cited above alone resulted in a scientifically flawed derivation of the PFOS MCL that is overly conservative."* (Chemistry Council of NJ)

RESPONSE: This comment is a summary of the commenter's other comments (above) that state that immune toxicity is secondary to hepatic effects and that dietary exposure is more appropriate than gavage exposure. These comments were addressed above.

6. Point of Departure (POD) from Dong et al. (2009)

COMMENT: *The decision to use the Dong 2009 data is further called into question by the results of the Subcommittee's benchmark dose (BMD) modeling which reveal that the SRBC response data failed to provide an acceptable fit to any of the dose-response models included in USEPA's BMD software. The inability of BMD modeling to yield a valid POD suggests that the SRBC response data reported in the Dong 2009 study are not sufficiently robust.* (American Chemistry Council)

COMMENT: *It also fails to provide its rationale for selecting the SRBC response data from Dong et al. (2009) to generate the MCL when they conflict with those reported by the same group in a subsequent study and by other researchers. The Subcommittee is similarly silent on its inability to fit the SRBC data from Dong et al. (2009) to any of the dose-response models included in USEPA's benchmark dose (BMD) software.* (American Chemistry Council)

RESPONSE: As discussed on page 246 of the Health-based MCL Support Document, a BMDL could not be calculated for the PFCR data from Dong et al. (2009), likely due to the steepness of the dose-response curve in the low dose range near the BMD. According to USEPA Benchmark Dose Modeling Guidance, a NOAEL or LOAEL is used as the POD when a BMDL cannot be developed. It is noted that the USEPA (2016) Health Advisories for both PFOS and PFOA are based on the NOAEL/LOAEL approach; BMD modeling was not used.

6. Use of serum PFOS levels as dose metric

COMMENT: *The elimination half-life in humans is several years, though some species are capable of excreting the substance more readily, thus complicating the reliance on rodent specifies in toxicology models.* (Philippe Grandjean)

RESPONSE: The Health Effects Subcommittee agrees that experimental animals excrete PFOS more rapidly than humans. Therefore, the same external dose results in a much higher internal dose (i.e. serum level) in humans than in animals. This interspecies

toxicokinetic difference is accounted for in the PFOS risk assessment by extrapolating from animals to humans on the basis of serum levels, rather than using the default uncertainty factor of 3 for interspecies toxicokinetics differences.

COMMENT: *Using serum PFOS levels as an indicator of internal exposure is appropriate since there is published literature demonstrating the dose-response relationship between the internal dose (serum in nanograms per liter (ng/l)) and effects, which is inconsistent with the administered dose (milligrams per kilogram per day) (mg/kg/d)). The latter is the result of many factors, including experimental design such as route of administration (diet versus gavage), as well as species and sex of experimental animals. However, the importance of the differences between the administered and internal dose was not discussed or weighted in DWQI's key study evaluation for quantitative determination of the NOAEL and LOAEL.* (Chemistry Council of NJ)

RESPONSE: The basis of this comment is unclear. The Health Effects Subcommittee agrees that using serum PFOS levels as an indicator of internal dose is appropriate. Serum level, as an indicator of internal dose, is used as the dose metric in risk assessments for PFOS and PFOA developed by other scientists and agencies. It is well accepted that internal dose is the appropriate exposure metric for risk assessment of long-chain perfluorinated chemicals such as PFOS, and internal dose is a more appropriate exposure metric for systemic effects of chemicals in general. This is because internal dose eliminates uncertainties associated with dose administration/intake, absorption, and distribution that are associated with dose-response metrics based on administered dose. The Health Effects Subcommittee is not aware of any implications of the differences between the administered and internal (i.e. serum concentration) dose that require discussion.

7. Development of Target Human Serum Levels

COMMENT: *DWQI fails to provide any context regarding the proposed Target Human Serum Level.* (Chemistry Council of NJ)

COMMENT: *DWQI compares predicted serum PFOA levels to background levels but fails to provide any context regarding the proposed Target Human Serum level. To this point, the health-based MCL derivation process as outlined in DWQI's Figure E-2 is inconsistent with internationally accepted processes to extrapolate hazard information in animals to humans for risk assessment purposes (such as the principles outlined in the IPCS Environmental Health Criteria Monograph no. 104). The process followed by DWQI is non-standard, in that it applies uncertainty factors directly to the animal data*

prior to adjusting to a human equivalent dose using a clearance factor. The derivation and choice of clearance factor is not well-described, nor is the rationale for choice of adjustment factor clear given the application of adjustment factor to the serum dose versus external dose (i.e. what are the pros and cons for accounting for TK differences under DWQI's process versus internationally accepted processes?)." (Chemistry Council of NJ)

RESPONSE: It is unclear why "serum PFOA levels" are mentioned in the comment on the PFOS Health-based MCL document. Furthermore, the interspecies extrapolation approach used by the Health Effects Subcommittee is not non-standard and is used in other PFC risk assessments, including the PFOA risk assessment presented by Tardiff et al. (2009). More importantly, the numerical result is identical when the serum level at the Point of Departure (NOAEL, LOAEL, or BMDL) from an animal study is converted to the equivalent human external dose before or after the uncertainty factors are applied. There is no need to discuss the "pros and cons" of the two approaches mentioned because they are mathematically identical. Finally, it is clearly stated in the Health Effects Support Document that the clearance factor, which relates serum PFOS level to human external dose, comes from the USEPA (2016) PFOS risk assessment.

8. Selection of Uncertainty Factors

COMMENT: *In this setting, where biological activity at very low doses are documented in animals and humans, and ongoing consequences to humans are also certain if exposures are permitted to persist, the New Jersey recommendation is reasonable based on current data. Because the scientific process for the PFAS has consistently shown that consequences of exposure are discovered over time, the uncertainty factor of 30 chosen by New Jersey scientists is a reasonable choice. (Environmentalists can reasonably argue for an uncertainty factor of 100 in this setting, and that would create an MCL of around 4 ng/L. Detection and accuracy are also very important goals of science and policy documents for hazardous environmental contaminants.) Everyone wants a standard that is achievable and provides safety for themselves and fellow members of affected populations. An MCL of 13 is a defensible standard from a policy perspective. It sets a threshold that is driven by scientific data concerning endpoints, and the proposed standard is reproducibly measurable, and achievable with current technology.* (Alan Ducatman)

RESPONSE: This comment supporting the uncertainty factors used in Health-based MCL development is acknowledged. However, it is emphasized that the Health-based MCL was developed independently of analytical detection and accuracy considerations. These factors were evaluated in the DWQI Treatment Subcommittee's development of

the Practical Quantitation Level (PQL).

COMMENT: *Although the RfD determined by NJDWQI is a significant departure from the much less protective RfD of 20 ng/kg/day developed by USEPA, we disagree with the UF (uncertainty factor) used to determine the target human serum level. NJDWQI applied a UF of unity (1.0) for sub-chronic versus chronic testing used in Dong et al (2009) even though this study of 60 days is of sub-chronic duration. Sub-chronic duration is > 30 day to ≤ 90 days. A UF of 10 is normally applied when sub-chronic is used instead of chronic testing to estimate a NOAEL.*

NJDWQI asserts that an uncertainty factor to extrapolate sub-chronic to chronic is not needed because the immunotoxicity studies of sub-chronic duration did not show a greater effect (response) at longer duration (but within the sub-chronic duration period) among the three studies reviewed. NJDWQI notes that for the same PFOS serum concentration of 1 x 105 ng/ml, plaque forming cell response decreased by the same 60% in two studies despite the difference in duration between these two studies, Zheng et al (2009) at 7 days duration and Dong et al (2009) at 60 days duration. NJDWQI asserts, therefore, that the decrease in plaque forming cell response does not progress at longer exposure duration. Although suggestive of a lack of progression over time, these tests are of very short duration (7-60 days) and would not fully explain whether this premise holds true at longer chronic durations of 6 months or more. Further, the mechanistic basis for the immunotoxic effect of PFOS is unknown, and whether further long-term exposures accelerate this effect.

Omission of a UF for sub-chronic-to-chronic in risk assessment should not be done on the basis of results taken solely from short term studies, especially without an understanding of the mechanism of toxicity. A UF should be applied. In lieu of some (limited) evidence of no increase in effect in dose-response between the 7-day and 60-day short-term sub-chronic studies applying a UF of 3 versus 10 is reasonable.

As indicated by NJDWQI, "serum PFOS levels in the general U.S. population are currently near or within the range of central tendency serum PFOS levels in the studies that found associations with decreased immune response (NJDWQI 2017). Median and 95% serum PFOS concentrations are 5.2 ng/ml and 19 ng/ml, respectively, in the general U.S. population (CDC-NHANES 2017). Decreases in vaccine response were found at serum levels 6 – 27 ng/ml (Grandjean et al. 2012; Granum et al. 2013; Kielsen et al. 2016; Stein et al., 2016), within the range of serum levels in the general population. Therefore, contribution of any additional PFOS from exposure to contaminated drinking water, irrespective of the MCL level chosen, may be inadequate to assure protection for these toxicity effects (immunotoxicity), especially in sensitive individuals and vulnerable

segments like infants and children. This uncertainty is broadly reflected in applying UFs to calculate MCLs.

A UF of 3 should be applied to extrapolate from sub-chronic to chronic testing in the Dong et al. (2009) study, to calculate a RfD and MCL, as follows:

A UF_{human} of 10 was used to account for increased sensitivity in sensitive sub-populations versus the average human population, and for general physiological and metabolic variation within the human population. A UF of 3 was used to account for interspecies (rodent to human) toxicodynamic differences. No UF is needed for toxicokinetic differences since the POD (point of departure), in this case the NOAEL, is based on blood serum PFOS levels. A UF of 3 is applied to estimate the NOAEL for chronic testing from sub-chronic testing used. Since individual UFs are as log-units the product of 3 x 3 is taken as 10. Therefore, the total UF applied is 100.

$$\text{Target Human Serum Level} = \text{POD (NOAEL)} \frac{674 \text{ ng/ml}}{\text{UF } 100} = 6.74 \text{ ng/ml}$$

The RfD (reference dose) is calculated as: target human serum level x clearance factor, where the clearance factor is the constant 1.8 x 10-5 derived by USEPA (EPA 2016b).
Reference dose (RfD) = 6.74 ng/ml x 1000ml/L x .000081 L/kg/day = 0.55 ng/kg/day

Summary of variables

NOAEL (POD)	*674 ng/ml*
total UF	*100 (10 UF_{human}, 3$UF_{subcronic\text{-}chronic}$, 3$UF_{interspecises\ toxicodynamic}$)*
Target human serum level	*6.74 ng/ml*
RSC	*0.20*
clearance factor	*0.000081 L/Kg/day*
default adult body weight	*70 kg per NJDWQI*
default adult water intake	*2.0 L/day per NJDWQI*

To compare with NJDWQI in its derivation, the MCL is calculated using adult default exposure values of weight and intake:

$$MCL = \frac{0.55 \text{ ng/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 3.85 \text{ ng/L (rounded to 4 ng/L)}$$

Adjusting the total UF to 100, the MCL calculated using NJDWQI variables should be 4 ng/L." (Delaware Riverkeeper Network)

RESPONSE: As reviewed by the commenter, an uncertainty factor (UF) for duration of exposure of 1 was used because studies with varying durations suggest that PFOS causes decreased PFCR within a short timeframe, and that this effect does not occur from longer exposure to lower doses. The use of serum PFOS levels for dose-response evaluation further support an UF of 1 for duration of exposure. Because the dose-response is based on serum PFOS levels rather than administered dose, application of an uncertainty factor to account for potential increases in serum PFOS levels with longer exposure durations is not necessary.

9. Calculation of Reference Dose

COMMENT: *Absent application of epidemiologic data, NJWQI's rigorous methodology and criteria used to select a BMDL, or NOAEL if applicable, is scientifically sound and conservative. Of the 4 final studies chosen by NJWQI for dose-response modeling, the Dong et al 2009 study of decreased plaque forming cell response, predictive of immunotoxicity, resulted in the lowest (most sensitive) point of departure (POD). As discussed in the report, the NOAEL of the study was used as the POD, or 674 ng/L, since BMDS software modeling would not calculate a BMDL for this study's dose-response data (NJDWQI 2017). After application of uncertainty factors the target human serum level calculated was the lowest among the 4 final studies, and resulted in the lowest RfD of 1.8 ng/kg/day.* (Delaware Riverkeeper Network)

RESPONSE: The Health Effects Subcommittee agrees with the commenter's summary of the derivation of the Reference Dose.

EXPOSURES TO THE FETUS, INFANTS, AND CHILDREN

1. A protective Health-based MCL will minimize public concern about exposure through breast milk

COMMENT: *Another is the consideration of infants who have been breast fed. This consideration is important because breast feeding is consistently shown to convey many health advantages to infants. Any contaminant exposure, such as PFOS, which may dissuade breast-feeding due to parental fears of contaminating infants and children is undesirable, costly, and a significant problem for both health and economic development of an affected geography. Setting a standard that minimizes this concern is in the public interest and economically sound.* (Alan Ducatman)

RESPONSE: The Health Effects Subcommittee agrees with the commenter that a protective drinking water standard for PFOS will help to assure the public that breast-fed infants will not be exposed to excessive PFOS levels from maternal exposure to contaminated drinking water.

2. Higher exposures in children than adults from non-drinking water sources

COMMENT: *There is evidence that young children are exposed to differential intakes of PFOS and PFOA because of age-specific behaviors, such as hand-to-mouth behavior, resulting in greater ingestion of house dust and dust on surfaces/products containing perfluorochemicals such as upholstered furniture, clothing, bedding, automobile fabrics, and carpets. These exposures are generally in addition to normal PFOS exposures from food and water, packaging, and a range of consumer products.*

Using NHANES data, Lorber and Egeghy found that incidental ingestion of dust is far less important among adults than children (Lorber and Egeghy 2011). Children dust intakes are highly variable due to the distribution of dust PFOA concentrations in homes; the 95th percentile intake from dust ingestion is about three times the intake from food ingestion (Lorber and Egeghy 2011). In another study by Egeghy and Lorber, the authors estimated that under typical exposure conditions, where exposure media concentrations are representative of background conditions, the median PFOS intake (sum of the median route-specific intakes) for 2-year-old children under typical exposure conditions was 50 ng/day (Egeghy and Lorber 2011). In the typical scenario for 2-year olds the contribution from ingested dust and ingested water were found to be nearly the same at 36% and 42%, respectively. Alternatively, for adults the contributions to PFOS daily intakes were much different, 6% for dust ingestion and 72% for food.

Under a typical scenario Egeghy and Lorber estimated a median total PFOS intake at 160 ng/day for adults. Under a contaminated environment scenario (contaminated water supply) they estimate median total PFOS intakes of 640 ng/day in 2-year olds and 2200 ng/day in adults. In either the typical scenario or a contaminated water scenario the authors estimated that the contribution of water to total PFOS intake is about the same in adults as in 2-year olds, about 20%. Using the authors median PFOS intake data and median weight for 2-year olds of about 13 kg (Table 8-12, Exposure Factors Handbook 2011), we calculate the median PFOS daily dose to 2-year olds at 3.85 ng/kg/day, and the median daily PFOS dose to adults (using a default 70 kg adult weight) at 2.29 ng/kg/day under the typical scenario. The 2-year old children PFOS daily exposure dose is therefore about 70% higher than adults. Both adults and children (2 year olds) median

daily dose under the typical exposure scenario would exceed the allowable reference dose (RfD) of 1.8 ng/kg/day proposed by NJDWQI for PFOS, double the proposed RfD in 2-year olds. (Delaware Riverkeeper Network)

RESPONSE: The Health Effects Subcommittee agrees that PFOS exposures to children from multiple sources, on a body weight basis, are likely to be higher than in adults. The data on non-drinking water exposures to PFOS reviewed by the commenter provides support for the 20% Relative Source Contribution factor used in the recommended Health-based MCL.

3. Exposures to the fetus and infant via maternal exposure

COMMENT: *In addition to greater environmental exposures than adults, children are burdened with PFOS at birth. "Evidence shows that PFOS is distributed within the body and can be transferred from pregnant women to their unborn children and offspring" (USEPA 2016b). PFOS has been quantified in umbilical cord blood, suggesting maternal transfer (Apelberg et al. 2007; Cariou et al. 2015; Tao et al. 2008; Völkel et al. 2008; Von Ehrenstein et al. 2009; USEPA 2016b). One study found PFOS at a mean of 1.28 ng/ml in 99 of 100 samples of cord blood (Cariou et al. 2015)*

PFOS is also transferred to children via breast milk. Cariou et al. 2015 found PFOS in 82% of breast milk samples at a mean concentration of 0.04 ng/ml. In a study of 70 human breast milk samples in patients from Germany and Hungary PFOS concentrations ranged from 0.028 to .309 ng/ml (Völkel et al. 2008; USEPA 2016b). PFOS transfer to infants during breast feeding lowers the mother's PFOS blood serum levels. In a study by Mondal et al. (2014) of 633 women and 49 infants each month of breast feeding was found to lower maternal serum PFOS levels by 3% and increase infant serum levels by 4%. Using the Cariou et al. (2015) mean breast milk PFOS concentration of 0.04 ng/ml and an upper percentile daily milk intake of 951 ml/day (table 15-3, USEPA 2008), we calculated daily PFOS intake from breast milk to breast fed infants 0 < 1 years at about 38 ng/day. Based on a 90th percentile body weight of 10.8 kg for infants 6 < 12 months age (table 8-3 USEPA 2008), the daily dose intake for this infant group of 0 < 1 years from breast milk is estimated at 3.5 ng/kg/day.

In summary, age-specific behaviors (e.g. hand-to-mouth) and exposures from placental transfer and breastfeeding, in addition to normal exposures from ingested water and food, increase the PFOS body burdens in young children. (Delaware Riverkeeper Network)

COMMENT: *We have shown that PFOS passes the placental barrier and that cord blood contains almost as much PFOS as the maternal blood. Most recently, we have shown that PFOS is excreted by the mother in milk during breastfeeding, thus causing the serum-PFOS concentration to increase substantially in breast-fed infants. I note that most of the epidemiological evidence has not focused on exposures during infancy, although early postnatal development must be considered a highly vulnerable period that must be taken into regard when determining exposure limits.* (Philippe Grandjean)

RESPONSE: The Health Effects Subcommittee agrees with the comments stating that maternal exposure to PFOS results in exposures to the fetus and breast-fed infant. As reviewed in the Health-based MCL Support Document, fetal PFOS blood levels are about half of maternal blood levels (p. 22), and serum levels in breast-fed infants reach levels several fold higher than in the mother (p. 23-26). These exposures are of concern because PFOS causes developmental effects and other effects from short term exposure, and they provide support for a health-protective approach in Health-based MCL development.

4. Use of child exposure values in Health-based MCL development

COMMENT: *"The RfD (reference dose) for PFOS (perfuorooctane sulfonate) derived by the NJDWQI (New Jersey Drinking Water Quality Institute) is the most stringent and protective in the U.S., based on a rigorous analysis of all available PFOS animal and epidemiologic toxicological studies. However, in its use of adult default exposure values to determine a maximum contaminant level (MCL), younger children would not be protected since younger children dose intakes would exceed the allowable RfD. This is disconcerting since existing PFOS serum levels in children in the normal population are already within or near the serum PFOS levels associated with immunotoxic effects found in epidemiologic studies. In addition, other toxic effects found associated with children and PFOS exposure may lead to increased potential for later disease manifestation. It is essential, therefore, that the NJDWQI depart from the typical use of adult default exposure values and use children's values. Using appropriate children exposure values, we recommend a MCL for PFOS of 5 ng/L.* (Delaware Riverkeeper Network)

COMMENT: *Some of the PFOS toxic endpoints to children have lasting effects and may subject children to later disease development. Deriving a MCL based on adult weights and water intakes results in a RfD imposed on children in excess of the maximum allowable 1.8 ng/kg/day. The uncertainty factor for sensitivity in the human population applied in the derivation accounts only for human variability in sensitivity to effect. To assure protection of children it is important that children specific weight and water intake exposure values be used in the MCL calculation.*

Body weight and water intakes of children ages 1-6 are used herein to determine a MCL. We use a mean body weight for this group of 16.8 kg and water intakes of 0.69 L/day mean, 1.19 L/day 90th percentile. Mean weight for the group 1-6 were determined using EPA 2011 Exposure Factor Handbook data for these ages, taking smaller increments of age groups and gender, combined by weighting the means of group increments, and pooling variances to determine means and standard deviations. We determined a 1.19 L/day composite water intake rate for children 1-6 at the 90th percentile, based on the lognormal distribution of water intakes for this combined age group, shown in the graph below.

[Figure was included in comment]

To compare the difference in MCLs derived by NJDWQI with that derived herein using children weight and water intakes, we use the same RfD of 1.8 ng/kg/day derived by NJDWQI (which excludes applying the uncertainty factor of 3 we used to estimate NOAEL chronic from subchronic testing).

Summary of variables used and values

RfD	*1.8 ng/kg/day*
RSC	*0.20*
children body weight	*16.8 kg*
children intake	*1.19 L/day 90th percentile*

Children Group (age 1-6)

$$MCL = \frac{1.8\ ng/kg/day \times 16.8\ kg \times 0.2\ RSC}{1.19\ L/day} = 5.08\ ng/L \text{ (round to 5 ng/L)}$$

(Using a mean water intake of 0.69 L/day results in a MCL of 8.8 ng/L)

The MCL for PFOS should be 5 ng/l.

If a UF of 3 to estimate chronic NOAEL from sub-chronic is included the MCL becomes:

$$MCL = \frac{0.55\ ng/kg/day \times 16.8\ kg \times 0.2\ RSC}{1.19\ L/day} = 1.55\ ng/L \text{ (round to 2 ng/L)}$$

(Delaware Riverkeeper Network)

COMMENT: *However, all population segments must be protected. Our analysis finds that at the proposed 13 ng/l MCL, PFOS daily intakes by body weight posed to young children 1-6 would be more than double the PFOS dose of 1.8 ng/kg/day deemed*

allowable by NJDWQI. This is disconcerting since existing serum PFOS levels in children in the population are already within or near serum PFOS levels associated with immunotoxic effects found in epidemiologic studies. The developing fetus, infants, and young children are particularly sensitive to PFOS and PFOA exposures during early sensitive periods. Early PFOS exposures in children, even at low doses of 1.8 ng/kg/day, may affect risk for later disease manifestation. To assure protection of children's health NJDWQI should depart from using adult default exposure values and use children specific exposure values in its MCL derivation, as described in this review. We recommend an MCL of 5 ng/L, as calculated above based on children exposure values. (Delaware Riverkeeper Network)

RESPONSE: It is acknowledged that infants and children have higher exposures to PFOS 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 PFOS exposures in young infants, the age group expected to have the highest exposure.

5. Other states' drinking water risk assessments consider higher infant exposures

COMMENT: *Other states have recognized children and infants as a more vulnerable population segment. Vermont used a 95th percentile body weight-adjusted water intake rate of 0.175 L/kg/day for the first year of life in its MCL calculation to determine a MCL of 20 ng/l. The MCL is applied as a sum combination, [PFOS + PFOA] ≤ 20 ng/l (Vermont 2016). In 2017 the Minnesota Department of Health (MDH) updated its earlier Health Risk Limit (HRL) for PFOS in drinking water. MDH used the USEPA RfD of 20 ng/kg/day based on animal developmental effects but incorporated a database uncertainty factor of 3 in recognition of immunotoxicity shown in animal studies. This resulted in a RfD of 5.1 ng/kg/day. MDH modeled two scenarios and found a breast-fed infant exposure scenario as most limiting, and determined a PFOS limit of 27 ng/L (MDH 2017)."* (Delaware Riverkeeper Network)

RESPONSE: The Health Effects Subcommittee is aware of the PFOS drinking water risk assessments developed by Vermont and Minnesota. The Subcommittee concludes

that Vermont's approach, while protective, is uncertain because the PFOS risk assessment is on steady-state serum levels from constant doses over many years, while infant exposures vary with age and occur over a period too short to reach steady-state. Minnesota used a Reference Dose of 5.1 ng/kg/day, modeling of exposure to a breast-fed infant, and Relative Source Contribution of 50% (instead of the more stringent default value of 20%) to derive a drinking water value of 27 ng/L. Using Minnesota's exposure assumptions with the Health Effects Subcommittee's Reference Dose of 1.8 ng/kg/day results in a drinking water value of 10 ng/L, which is very close to the recommended Health-based MCL of 13 ng/L.

CANCER RISK ASSESSMENT

COMMENT: *At the onset, it is appropriate that the MCL be based on the noncancer endpoints, but not for the reasons provided in DWQI's PFOS Health Effects Subcommittee Report. For the cancer endpoint, a cancer slope factor was derived from the incidence of hepatocellular tumors in female rats only as male rat data was "uncertain" because the tumor occurrence was at high dose only (Butenhoff et al., 2012). The importance of this finding was missing in the mode of action (MOA) assessment for PFOS in this document. Based on the Butenhoff et al., 2012 feeding study documentation of tumor formation in high dose female and male rats (20 parts per million (ppm)), other important non-neoplastic, adaptive changes occur in the liver, including hepatocellular hypertrophy with proliferation of endoplasmic reticulum, vacuolation, and increased eosinophilic granulation of the cytoplasm in both males and females at the higher exposure concentrations. These findings are consistent with a threshold MOA due to chronic cellular injury, repair and proliferation. However, the document focused only on the role of peroxisome proliferator activated receptor alpha (PPARα), which is only one of many potential mechanisms for the histopathological sequela of events leading to tumor formation because of chronic cell injury* (Chemistry Council of NJ).

RESPONSE: As discussed in the Health-based MCL Support Document, the mode of action (MOA) for PFOS-mediated carcinogenicity is not known. The occurrence of a variety of non-cancer hepatic effects as well as hepatocellular tumors does not constitute evidence that these non-cancer and cancer effects are causally related. While there is little to no evidence that PFOS is either mutagenic or genotoxic, this does not imply a threshold for carcinogenicity. Furthermore, the observation of tumors only at a high dose does not necessarily imply the lack of carcinogenic potential at lower doses. Failure to observe a tumorigenic response at lower doses can result from the inherent statistical limitations of the assay resulting related to the sample size at each dose. In addition, we note that while liver tumors were only observed at the highest dose in males, liver tumors were observed at the both the highest administered dose and in the recovery dose, each

resulting in a different AUC serum PFOS concentration, in females. According to USEPA (2005) cancer risk assessment guidelines, the cancer risk assessment is based on linear no-threshold extrapolation (i.e. a cancer slope factor) when the MOA for carcinogenicity is not known. Finally, discussion of the potential role PPARα was presented only from the standpoint of providing evidence that PPARα was *not* a likely MOA. Other possible cancer MOAs were discussed, but there was insufficient evidence for any MOA to consider alternative dose-response approaches for the cancer endpoint.

COMMENT: *The threshold or noncancer approach is supported by the high dose and one sex/species finding, in addition to the lack of significant tumor formation in the recovery group, indicating that once exposure (and cell injury) is terminated, progression to tumor formation does not occur. Thus, if the noncancer endpoint (liver injury) can be prevented, the cancer endpoint will not develop. In addition, the threshold and, thus, noncancer endpoint risk assessment method application is consistent with the lack of mutagenicity or genotoxicity in PFOS studies* (Chemistry Council of NJ).

RESPONSE: Contrary to the assertion of the commenter, liver tumors were, in fact, observed in both sexes of rats. Although the tumor incidence in the recovery group of either sex was not statistically significantly different from controls, the test for trend (including the recovery group) was statistically significant for females. Additionally, the female tumor incidence in the recovery group was well predicted by several standard dose-response models that also provided a good fit for the high dose tumor response. Although the PFOS concentration in the feed was identical in the high dose and recovery groups, the shorter exposure duration in the recovery group resulted in a lower average daily dose (mg/kg/day) during the two year study period than in the high dose group. The lower tumor incidence and lack of statistical significance in the recovery group for both sexes is consistent with the lower average and overall dose (i.e. AUC) in this group, and does not necessarily indicate that progression to tumors stopped when dosing with PFOS. In contrast, the time course of development of tumors in the recovery group (females) is not known, and the observed tumors could have developed after dosing ended (i.e., in the recovery phase). Finally, even if it were known that no tumors occurred after dosing in the recovery group ended, this observation would not be relevant to determination of human cancer risk, which is calculated based on exposure throughout the lifetime.

COMMENT: *In regard to carcinogenicity, less evidence is available on PFOS than on PFOA, but the absence of evidence is of course not evidence that a cancer risk is absent. The risk assessment for cancer carries out by the NJ Subcommittee relies on experimental animal evidence and appears to be appropriate, except that it does not consider any increased vulnerability during early development.* (Philippe Grandjean)

RESPONSE: The evidence for the carcinogenicity of PFOS is currently confined to one species in a single study. This is consistent with the designation under USEPA (2005) Guidelines for Carcinogen Risk Assessment (USEPA, 2005) of "suggestive evidence of carcinogenicity." According to USEPA (2005) Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, cancer risk estimates are adjusted to for higher risk during early life stages only for chemicals that are carcinogenic by a mutagenic MOA. As discussed above, there is no evidence that PFOS causes tumors through this MOA.

MODE OF ACTION

COMMENT: *DWQI's document would be much improved by synthesizing the database when assessing the weight of evidence, MOA, and relevance to human exposures consistent with USEPA guidance, including Framework for Determining a Mutagenic Mode of Action for Carcinogenicity and International Program on Chemical Safety (IPCS) Mode of Action Framework (for cancer and noncancer risk assessment)"*
(Chemistry Council of NJ)

RESPONSE: The USEPA document cited by the commenter is not relevant, since the Health-based MCL Support Document clearly concludes that there is no evidence to indicate that PFOS is carcinogenic through a mutagenic mode of action. However, it is emphasized that the USEPA (2005) cancer risk assessment guidance does not specify that a cancer slope factor is developed only if a mutagenic mode of action is demonstrated. In contrast, development of a slope factor is the default approach to be used unless a threshold mode of action is established. The Health Effects Subcommittee is aware of the IPCS "Mode of Action Framework." It is noted that the 2008 version of this guidance states, "As in the cancer Human Relevance Framework (HRF), the first step is to determine whether the weight of evidence based on experimental observations is sufficient to establish a hypothesized MOA." A 2013 update to this guidance states that "… mode of action analysis is envisioned as an iterative hypothesis generating and testing process that defines how to assess or test strategically based on risk management needs," and that "the mode of action framework addresses two key questions. The first is whether there are sufficient data to hypothesize, with an acceptable level of confidence, a mode of action for a known or suspected toxicological outcome. The second is the extent to which such a mode of action would or is likely to operate in humans at relevant exposure levels (species concordance analysis)."
Consistent with the IPCS framework, the Health Effect Subcommittee has summarized the available information on the mode of action for the critical endpoints identified in its PFOS assessment. As stated in the Health-based MCL Support Document, it is concluded that there is insufficient available information to "hypothesize, with an acceptable level of confidence a mode of action" for either immunosuppression or

hepatocellular tumors resulting from PFOS exposure. This conclusion is supported by the NTP (2016) report "Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate" which states that, "Although the mechanism(s) of PFOS-associated immunotoxicity is not well understood, suppression of the antibody response and NK cell function are both potential mechanisms by which PFOS may reduce disease resistance." Based on both the similarity of rodent and human immune systems and the supporting human epidemiology data (i.e., "species concordance"), the Health Effects Subcommittee conclude that the mode of action underlying immunosuppression in mice, while unknown, is "likely to operate in humans at relevant exposure levels." According to the IPCS framework, the next step in the "iterative hypothesis generating and testing process" would be focused testing to support the several possible and speculative mode of action hypotheses that could be generated. While the Health Effects Subcommittee would support such mode of action studies, it is clear that the present state of knowledge does not permit proceeding further within the IPCS framework.

HUMAN EPIDEMIOLOGY

1. Epidemiological data on decreased immune response

COMMENT: *The early findings in mice spurred an interest in pursuing the antibody outcomes in epidemiological studies. In fact, an international working group had recommended this approach as a valid and clinically relevant methodology in human immunotoxicological research. The advantages include the fact that a vaccination constitutes a natural and highly feasible experiment of antigen exposure, where the same dose of antigen is applied at the same age, 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 PFOS and related compounds. Our findings show an inverse association of serum-PFOS concentrations with the response to booster vaccination in children and adults, this suggesting a deficit in the B cell reactivation by T 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 using human white cells, although experimental studies have not yet revealed the detailed mechanisms.*

The adaptive immune system is at first dominated by Th2 responses, Th1 responses mature during infancy to allow proper responses to infections and routine immunizations. Allergy and asthma are characterized by a Th2-biased immune response, and increased odds of asthma in children were reported at elevated PFAS exposures, although this finding has not been replicated. The lack of clear evidence on PFAS-associated allergy

may in part be due to uncontrolled and variable allergen exposures and the absence of well-defined outcome variables comparable to the vaccine-induced antibodies used to assess Th1 activity. Also, previous vaccination with attenuated virus plays an important role. I also note that breastfeeding is generally considered advantageous for the child's immune system development, although the evidence is somewhat equivocal, perhaps because very few studies have taken into regard the inverse effects of immunotoxicants present in human milk. Our studies of PFAS-exposed children show no clear benefit of breastfeeding, perhaps as a result of human milk acting as a vehicle for immunotoxicants that counteract any benefits.

From our study published in JAMA, I would like to emphasize that many 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 disease despite a total of four vaccinations. We calculated the odds ratios (ORs) for a doubling in the child's age-5 serum-PFOS concentration as a predictor of having an antibody concentration below 0.1 IU/mL at age 7 years. The ORs for tetanus and diptheria were 2.38 and 2.61, both of borderline statistical significance. When looking at the antibody concentration before the age-5 booster, a doubling in the prenatal PFOS exposure showed an OR of 2.48 for diphtheria, which was highly significant, although not for tetanus. When we used a structural equation model that allowed us to combine the two serum-PFOS concentrations at ages 5 and 7 years, we found that a doubled serum concentration of PFOS, combine with PFOA and PFHxS, was associated with an approximate decrease by 50% of the overall vaccine antibody concentration. (Philippe Grandjean)

RESPONSE: The Health Effects Subcommittee is aware of the human studies of effects of PFOS on the immune system that are summarized by the commenter. All of these studies are reviewed in the Health-based MCL Support Document.

COMMENT: *A study in children of the Faroe Islands found an inverse relationship in immune response with exposure to perfluorinated alkyl acids (Grandjean et al. 2012, Grandjean and BudtzJørgensen 2013), with maternal cord PFOS levels negatively correlated with anti-diphtheria antibody concentration at 5 years. Children in this population demonstrated increased odds of not reaching protective antibody levels for diphtheria after vaccination at 7 years old (Grandjean et al. 2012). The relevance of these findings to other populations is questionable, however, as increased exposure to other potential immunosuppressants was not accounted for in the study.* (American Chemistry Council)

RESPONSE: It is not clear what the commenter is referring to. In Grandjean et al. (2012), the authors state that, "We also considered the possible effect of PCB exposure, birth weight, maternal smoking during pregnancy, and duration of breastfeeding, in regard to their possible influence on the PFC regression coefficients." They also state that "Most of the PFCs correlated only weakly with PCBs in maternal serum." Potentially confounding immunosuppressants were also addressed in Grandjean et al. (2017) through sensitivity analyses. (Citation: Grandjean, P. 2017. Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. J. Immunotoxicol. 14: 188-195.)

COMMENT: *Five key epidemiology studies evaluated potential impacts of PFOS exposure on immune suppression (infectious disease and vaccine response). As with the animal data, the human data are inconsistent, as noted by Health Canada which concluded that "associations are observed between PFOS levels and decreases in antibodies against some (but not all) illnesses and the influence of PFOS exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous." Health Canada further noted that, while the available animal and human data may indicate immune system changes, "it is unclear whether small variations in these measures are sufficient to result in adverse health effects in humans."* (American Chemistry Council)

RESPONSE: The studies of vaccine response differ in the ages at which PFOS exposure and vaccine antibodies were measured, the time between inoculation and the measurement of antibody levels, the specific vaccines that were evaluated, the study populations, and the study design. Nevertheless, the observation of an association of decreased vaccine antibodies with some measure of PFOS exposure for at least one vaccine antibody in most of the studies is suggestive of an association between increased PFOS serum levels and decreased antibody response across different populations and different study designs. Further, given the different inherent antigenicity of different vaccines, there is no *a priori* reason to expect that the effect of PFOS exposure on all vaccine antibodies will be consistent. In regard to associations with infectious disease, Impinen et al. (2018), Dalsager et al. (2016), and Goudarzi et al. (2017) noted above were not available to Health Canada in its review. These more recent studies of clinical disease and PFOS exposure are consistent with the results of the studies of vaccine antibodies and PFOS exposure. Combined, they provide strong evidence that PFOS exposure in the general population can cause immunosuppression at the clinical level.

COMMENT: *After reviewing the available human data, Health Canada concluded – Although some effects on the antibody response have been observed, conflicting results were common in the dataset, which remains relatively small. A low level of consistency*

was observed across studies, with variations between genders, specific microbial immunoglobins, infections, mother vs. child exposure, and child years, amongst other characteristics. Moreover, the risk of residual confounding, bias, and chance cannot be discarded. These flaws impede concluding on a causative mechanism, and the nature of the association remains unclear. (American Chemistry Council)

RESPONSE: The Health Effects Subcommittee does not agree with the Health Canada's assessment that was presented by the commenter. Additionally, it is emphasized that the human epidemiology data are not used as the primary basis for the Health-based MCL. The primary focus of the Health Effects Subcommittee's risk assessment is on the controlled animal experiments that show a clear cause-and-effect relationship between serum PFOS concentrations in mice and decreased response to a foreign antigen (SRBC). Based on these studies, it is clear that immunosuppression is a valid and adverse endpoint for PFOS exposure. The epidemiology data provide support for the relevance of the animal data to human environmental exposure. In four of five human studies in different populations, PFOS exposure levels prevalent in the general population were significantly associated with decreased response to at least one vaccine. In three studies in different populations, exposures to PFOS at levels prevalent in the general population were significantly associated with increased risk/incidence of infectious disease in children, including hospitalization for infections in girls. As such, we conclude that the epidemiology data strongly support the conclusion that exposure to PFOS at current population levels can lead to immunosuppression. This conclusion is supported by NTP (2016) which concludes, "The evidence indicating that PFOS suppresses multiple aspects of the immune system supports the overall conclusion that PFOS alters immune function in humans." The Target Human Serum Level derived from the Dong et al. (2009) study falls within the range of central tendency serum PFOS concentrations from these human studies. Although the specific mechanisms that can explain differences in responses between sexes, across different vaccines, different types of infections, or different ages at which PFOS exposure is measured are not yet clear, it is more noteworthy PFOS is associated with immunosuppression in humans at general population exposure levels in a variety of populations, across a variety of vaccines, and for a variety of infections. While these human data do not easily lend themselves to quantitative dose-response analysis, such quantitative analysis is not necessary to establish the qualitative relevance to humans of the Health-based MCL derived from the animal database.

COMMENT: *Finally, a cohort of 411 adult members of the C8 Health Project in West Virginia was evaluated to determine whether there was an association between serum PFOS levels and antibody response following vaccination with an inactivated trivalent influenza vaccine (Looker et al. 2014). Vaccine response, as measured by geometric*

mean antibody titer rise, was not affected by PFOS exposure. (American Chemistry Council)

RESPONSE: We agree that Looker et al. (2014) did not show an association between PFOS exposure and influenza vaccine response. However, this was the only study identified by the Health Effects Subcommittee that did not show an association between PFOS exposure and decreased response to at least one vaccine.

We note that Looker et al. (2014) investigated a single vaccine (influenza). The only other study to investigate a possible association between PFOS and influenza vaccine was Granum et al. (2013). This study also found no association for influenza vaccine, although there was a statistically significant association between PFOS exposure and decreased response to rubella vaccine. It is well known that different vaccines and different preparations of the same vaccine have different inherent antigenicity. Therefore, it is not unexpected that PFOS exposure may not be associated with decreased response to a given vaccine. Additionally, this was the only study that investigated vaccine response in adults, and it is possible that effects of PFOS differ in children and adults.

2. Clinical significance of human epidemiology data on immune system effects

COMMENT: *The question has been raised whether our use of antibody responses to vaccinations is appropriate for establishing exposure limits to prevent adverse effects. One could argue that changes in antibody concentrations are subclinical and of questionable relevance to long-term health. On the other hand, this routine outcome reflects immune functions that may well be of relevance to resistance toward infections and to other immune-associated abnormalities. As already, outlined, antibody concentrations pose substantial advantages in epidemiological research, and they constitute a well-established indicator of complex immune functions. Deviations in this immune function biomarker at the individual level may then be linked to important shifts in the prevalence of related diseases at the population level – changes that would be apparent only in large prospective studies. Calculations have shown decreases in antibody concentrations of up to about 50% at a doubled PFAs exposure within the range of background exposures. Such decreases are not trivial, and effects of this magnitude would otherwise be expected only with exposures to such factors as ionizing radiation and cytostatic cancer drugs.*

In children, a relevant outcome that may be the result of poor antibody responses is the frequency of infections. Although infectious disease during childhood is often associated with housing conditions, daycare, the presence of siblings at home and other factors that may be difficult to adjust for in statistical analyses, two studies have examined this

possible connection. First, in a small group of Norwegian children, a positive association was seen between the maternal serum-PFOS concentration at childbirth and the number of episodes of common cold and gastroenteritis in the children, as assessed by questionnaire.

A more recent study of 359 Danish children aged 1-3 years obtained information from the mother on the presence of fever and symptoms in the child every two weeks for one year via test messages. The mother's early-pregnancy serum-PFOS concentration was a strong predictor of the child's incidence of infections, where a PFOS in the high tertile compared to the low tertile was associated with an increased proportion of days with fever (IRR: 1.65 (95% CI: 1.24, 2.18), p for trend <0.001). Further, higher PFOS concentrations were associated with increased numbers of episodes of co-occurrence of fever and coughing and fever and nasal discharge during the one-year study period. These observations suggest that our findings in regard to specific antibodies as markers of immune system functions are clinically relevant. Again, these findings document the public health implications of PFOS exposures in the general population, the plausibility of which are demonstrated by experimental toxicology reports." (Philippe Grandjean)

COMMENT: *"In its 1,100-page support document, the Subcommittee asserts the relevance of reduced SRBC response observed in mice to reduced resistance to infection in humans in explaining its rationale for its proposed MCL. Yet, the human studies generally report no increase in infection in children or adults and both USEPA and Health Canada have questioned whether the small variations in the antibodies observed in the available studies are sufficient to result in adverse health effects in humans.* (American Chemistry Council)

COMMENT: *Increased PFOS exposure was associated with decreased antibodies against rubella in children from a prospective birth cohort of pregnant women from Norway in a 2013 study by Granum et al. 2013. In contrast, prenatal exposure to PFOS was not associated with hospitalizations for infections in a 2010 Danish cohort study by Fei et al. nor with episodes of common cold, gastroenteritis, eczema or asthma in the Norwegian cohort (Granum et al. 2013).* (American Chemistry Council)

RESPONSE: The Health Effects Subcommittee agrees with the conclusion of the first commenter cited above (P. Grandjean) that the studies that he presented provide support for the public health significance of decreased immune response (as indicated by decreased vaccine response) associated with PFOS. All of these studies are described in the Health-based MCL Support Document. Fei et al. (2010) found a significant association between hospitalization for infection and PFOS exposure in girls. We note that hospitalization for infections implies a severe illness. Such an association with

PFOS exposure, even for one sex, should be considered to be highly significant from the standpoint of public health. Three additional studies relevant to this endpoint were recently identified by the Health Effects Subcommittee and have been added to the Health-based MCL Support Document. (Dalsager et al., 2016; Goudarzi et al., 2017; and Impinen et al., 2018). These three studies show associations of infectious disease with PFOS exposure and provide additional support for association between PFOS and infectious disease.

In addition to Granum et al. (2013) mentioned in the comment, two other studies also did not find an association of infectious disease and PFOS exposure (Okada et al, 2012 and Looker et al., 2014). However, it is noted that sample size in these studies was quite small, resulting in low power to detect an association. In summary, while there are mixed findings from studies of PFOS exposure and infectious disease, the four studies with positive results (Fei et al., 2010; Dalsager et al., 2016; Goudarzi et al., 2017; and Impinen et al., 2018) provide supportive evidence for such an association.

3. Immune system effects other than immunosuppression

COMMENT: *In a Taiwanese cohort study, the median serum PFOS concentration was significantly higher in asthmatic children (Dong et al. 2013) and prenatal exposure to PFOS was positively correlated with cord blood Immunoglobulin E (IgE) levels, particularly in male children. However, Wang et al. (2011) found no association with atopic dermatitis. Cord blood IgE levels, food allergy, eczema, wheezing, or otitis media were not associated with maternal PFOS in female infants in a prospective cohort study of pregnant women in Japan (Okada et al. 2012).* (American Chemistry Council)

COMMENT: *As the National Toxicology Program (NTP) notes in its review of PFOS the "effects on diverse endpoints such as suppression of the antibody response and increased hypersensitivity may be unrelated.*" (American Chemistry Council)

RESPONSE: The Health Effects Subcommittee's evaluation focused on immunosuppression as indicated by decreased vaccine response and the closely related endpoint of increased risk/incidence of infectious disease. As noted by NTP (2016), asthma, allergies, and eczema are hypersensitivity responses of the immune system. Such responses are qualitatively distinct from the immunosuppressive endpoints (i.e., decreased PFCR, decrease vaccine antibody levels, increased incidence of childhood infections) that were identified as being associated with PFOS. Furthermore, decreased PFCR, the endpoint that forms the basis for the Health-based MCL, is mediated by IgM, while, as noted by NTP (2016), hypersensitivity reactions are mediated by IgE. Therefore, there is no *a priori* reason to expect that

immunosensitization/hypersensitization reactions would be associated with PFOS exposure. The lack of consistent association with these other immune system endpoints does not diminish the significance of the observed associations of PFOS exposure with immunosuppression.

4. Epidemiology data for endocrine and reproductive effects, and for studies in children

COMMENT: "*Endocrine disruption and reproductive toxicity has been documented in substantial detail in mouse studies. As an indication of endocrine disruption, studies at NIEHS have shown delayed breast development at elevated exposure to perfluorinated compounds. Although this evidence mainly relates in PFOA, human studies show that the duration of breastfeeding is significantly shorter in women with high serum-PFOS concentrations. In our study, a doubling in the serum-PFOS concentration was linked to a decrease in breastfeeding duration by about 6 weeks – a very substantial and statistically significant decrease. Supporting findings were published from a U.S. cohort, thus suggesting that this association is of concern at current PFOS exposure levels. In a report that will be published in PLoS Medicine in late February, we show that baseline serum-PFOS concentrations predict the body weight increase following a six-month calorie-restriction diet. The results also showed that the metabolic rate was inversely associated with the PFOS concentration. Similar results were obtained for PFOA. In another study, also in press, we show that elevated serum-PFOS concentrations in serum obtained from American nurses in the late 1990s were associated with the risk of developing type 2 diabetes in subsequent years. Given the paucity of experimental toxicology findings exploring these high relevant outcomes, reliance on human data is crucial. Likewise, subfecundity has been reported at higher serum-PFOS concentrations in populations with background exposures. Again, this outcome is of major public health relevance, but may not be appropriately disclosed in animal models applied so far.*" (Philippe Grandjean)

COMMENT: *Epidemiologic studies have shown many associations between PFOS and PFOA exposure and health effects in children. A systematic review by Rappazzo et al. (2017) summarized the epidemiologic evidence (literature) for relationship between prenatal/childhood perfluorochemical exposure and health outcomes in children. They conclude: "there is evidence for positive associations between PFAS (perfluoroalkyl substances) and dyslipidemia, immunity (including vaccine response and asthma), renal function, and age at menarche", as described below (*Rappazzo et al. 2017).

A study by Geiger et al. (2014) in adolescents from NHANES data, found increases in PFOA, PFOS, or total PFAS serum concentrations positively associated with high total cholesterol (>170 mg/dL) and high LDL-C. Results in a study of 12,476 children and

adolescents found that PFOA was significantly associated with increased total cholesterol and LDL-C, and PFOS was significantly associated with increased total cholesterol, HDL-C, and LDL-C (Frisbee et al. 2010). Several other studies support dyslipidemia effects from exposure to PFCs in children (Rappazzo et al. 2017).

Delayed onset of puberty has been associated with altered risk of adult disease: diabetes mellitus, heart disease, bone disease, substance abuse, and asthma" (Rappazzo et al 2017). A C8 cross-sectional analysis of 3076 boys and 2931 girls found later age of puberty in both boys and girls associated with serum PFOS and PFOA levels (Lopez-Espinosa et al. 2011). For boys in that study "there was a relationship of reduced odds of reached puberty (raised testosterone) with increasing PFOS (delay of 190 days between the highest and lowest quartile)". In girls,"higher concentrations of PFOA or PFOS were associated with reduced odds of postmenarche (130 and 138 days of delay, respectively)". Delayed onset of puberty associated with PFOS and PFOA levels in epidemiologic studies is supported by animal studies. For example, PFOA was found to cause delayed mammary gland development in female mice offspring (White et al. 2011).

A limited number of studies have shown associations between renal function and serum PFC levels. Decrements in estimated glomerular filtration rate (eGFR) were found to be associated with increases in PFOA and PFOS concentrations in a large community study of 9660 children age 1<18 years (Watkins et al. 2013). The study population was children and adolescents highly exposed to PFOA from contaminated water supplies, but exposed to levels typical of PFOS, PFNA, and PFHxS in the normal population. Another cross-sectional analyses of NHANES 20032010 data of 1960 adolescents aged 12-19 years found PFOS and PFOA associated with a reduction in kidney function and increased uric acid levels (Kataria et al. 2015). The authors found that adolescents in the highest PFOA and PFOS quartile had a lower eGFR (estimated glomerular filtration), 6.84 mL/min/1.73 m2 (95 % CI: 2.19 to 11.48) and 9.69 mL/min/1.73 m2 (95 % CI: -4.59 to 14.78), respectively, compared to the lowest quartile. However, the authors note that reverse causality and residual confounding could explain their findings.

As described in the Introduction, three epidemiologic studies found suppression of vaccine mediated antibody response to be associated with PFOS and PFOA exposure in children. The study by Grandjean and Budtz-Jørgensen (2013) found an association between increases in serum PFOS and PFOA levels and decreases in serum antibody concentrations against tetanus and diphtheria toxoids in young children (follow-up of a Faroese birth cohort). A study in Norway of 99 participants found an inverse association between the level of anti-rubella antibodies in children's serum at age 3 years and the concentrations of PFOS, PFOA, PFNA, and PFHxS (Granum et al. 2013). A recent large cross-sectional study by Stein et al (2016) of 1191 children 12-19 years old using

NHANES data (1999-2000 and 2003-2004) found that a doubling of PFOS serum concentration was associated with a 7.4% (95% CI: -12.8, -1.7) decrease in mumps antibodies. A doubling of PFOS serum concentration was also associated with a 13.3% decrease in rubella antibodies; this association occurred among seropositive individuals (Stein et al. 2016).

PFOS serum levels in children associated with these immunosuppressive effects, found in these studies, are within or close to the PFOS serum levels found in the normal population. (Delaware Riverkeeper Network)

RESPONSE: The DWQI Health-based MCL Support Document for PFOA includes a detailed reviewed of the studies showing that PFOA causes delayed mammary development in mice. Additionally, the PFOS Health-based MCL document reviewed the epidemiology studies in children and adults that provide some evidence of an association of PFOS with the endpoints mentioned by the commenters. The Health Effects Subcommittee identified decreased vaccine response, elevated serum uric acid/hyperuricemia, and increased total cholesterol as the only human endpoints with sufficient evidence to be clearly associated with PFOS for the purposes of drawing conclusions for Hazard Identification. With additional confirmatory studies, the evidence linking additional endpoints to PFOS exposure may support their clear identification as a hazard.

5. Use of human data in quantitative risk assessment

COMMENT:

- *I wish to respond to the Drinking Water Quality Institute request for public input on the perfluorooctane sulfonate (PFOS) document (link provided). My main concern is that the very comprehensive Report summarizes much of the epidemiological evidence but in its conclusions completely ignores the human data when establishing a limit for PFOS in drinking water. While I understand that there is a regulatory tradition of relying on experimental toxicology information, it is inappropriate to ignore substantive evidence on human toxicity. My estimate is that the proposed limit for PFOS is 100-fold too high and therefore far from protective of human health.* (Philippe Grandjean)

- *In conclusion, while I understand that the DWQI must primarily rely on experimental toxicology data, I am surprised that the DWQI has disregarded the extensive epidemiological evidence when estimating safe exposure levels for PFOA in drinking water. The difference between species in regard to PFOS toxicokinetics and toxicity are well established, and the above calculations clearly show that these differences have not been appropriately taken into account. In addition, developmental exposure likely*

represents the main risk to humans, and the DWQI to some extent ignores this consideration. Likewise, the reliance on fairly crude outcomes in toxicology studies fails to acknowledge the importance of less serious outcomes, such as vulnerability to infectious disease, metabolic abnormalities, or subfecundity. Similar concerns were recently raised in a more general sense by scientist from the U.S. EPA, who concluded that "to protect public health more effectively, future risk assessments will need to use the full range of available data, draw on innovative methods to integrate diverse data streams, and consider health endpoints that also reflect the range of subtle effect and morbidities observed in human populations. (Philippe Grandjean)

- *For these reasons, I conclude that prudent risk assessment for PFOS should take into regard both animal data and human data, especially in the present context where a water limit relying on animal data alone appears to be at least 100-fold above the limit that would result if relying on human data.* (Philippe Grandjean)

COMMENT:

- *It is critical for children and vulnerable populations that the MCL be protective from the known health impacts of PFOS exposure. In setting the health advisory level of 70ng/L, the EPA did not consider recent studies that would have resulted in lower health advisory levels. Of particular concern was the lack of incorporation of human epidemiologic evidence of PFOS' impact on the immune system and its ability to reduce effectiveness of vaccines in children. Unlike the EPA, the DQWI utilized the immune system as the critical endpoint of concern in proposing a drinking water limit significantly more protective than the EPA health advisory. But the DWQI relied on mouse data instead of human exposure and human health impacts in setting the proposed MCL.*

  In the past decade, EWG has published many reports on the health impacts of PFC exposure, with a focus on PFOA and PFOS. EWG has detailed the history of use for these chemicals and reviewed the scientific evidence of the health impacts that may be occurring at environmentally relevant concentrations. EWG has also analyzed the drinking water testing results from New Jersey and the nationwide water sampling results collected through the Unregulated Contaminant Monitoring Rule that were compiled into an online interactive map.

  (1) The DWQI should use human epidemiologic evidence of health impacts to set the MCL

  EWG is supportive of the scientific analysis and the identification of immunotoxicity as the most sensitive endpoint based on the current evidence. EWG argues that the DWQI should utilize the human studies to set a health protective MCL and ensure that exposure

to drinking water does not increase risk above a health-protective threshold. Using the human epidemiologic health impacts would have resulted in a health protective value of 1 ng/L or lower. EWG agrees with the DWQI statements that:

Among the epidemiologic studies, the studies of immune effects, and most particularly those investigating effects on vaccine response, were generally consistent in showing adverse responses to PFOS.

and:

The observation of decreased resistance to childhood diseases in association with low, general population levels of PFOS exposure, and the consistency of this effect with a directly analogous outcome from animal studies, decreased plaque forming response, emphasizes the practical public health significance of PFOS-mediated immunosuppression." (Environmental Working Group)

- *We advise the DWQI to utilize the epidemiological evidence of reduced immune suppression at current general population exposure levels to eliminate any additional exposure from water.* (Environmental Working Group)

COMMENT: *Human epidemiologic data have current limitations and are not used as a quantitative basis for a health-based RfD and MCL. However, a RfD based on quantitative epidemiologic data for an immunotoxic effect should be taken into account. In our review of the New Jersey 2016 proposed standard for PFOA we derived a MCL based on the Grandjean and Budtz-Jørgensen (2013) study where benchmark calculations based on regression modeling enabled a determination of a BMDL. Based on that study's BMDL we calculated a 0.03 MCL for PFOA (Oliaei and Kriens 2016). Using the same methodology, we derive a MCL for PFOS as follows:*

The lower one-sided 95% confidence limit of the BMD, the BMDL (benchmark dose level) determined in the Grandjean and Budtz-Jørgensen (2013) study, is approximately 1.3 ng/ml for PFOS, based on the linear slope model of the regression. Based on the immunotoxic effects shown in this study we propose a 1.3 ng/ml BMDL for PFOS as the target human serum level. An uncertainty factor of 10 for human variation in susceptibility is applied. A clearance factor of 8.1 x 10-5 L/kg/day derived by USEPA for PFOS (USEPA 2016b) is applied to the target human serum Level to calculate an RfD.

$$RfD = \frac{1.3\ ng/ml \times 1000\ ml/L}{UF\ 10} \times 8.1 \times 10\text{-}5\ L/kg/day = 0.01\ ng/kg/day$$

Using NJDWQI default adult exposure values of 70 kg body weight, 2 L/day water intake, and a relative source contribution of 0.2, the MCL is:

$$MCL = \frac{0.01\ ng/kg/day \times 70\ kg \times 0.2\ RSC}{2\ L/day} = 0.07\ ng/L\ \ (round\ to\ 0.1\ ng/L)$$

This RfD is considerably more protective than the USEPA RfD of 20 ng/kg/day based on animal developmental effects (e.g. decreased pup body weight) (USEPA 2016b). However, because of potential increased susceptibility during pregnancy and lactation EPA used drinking water intake and body weight exposure values at the 90% distribution for lactating women, moderating the calculation (versus use of adult default weight and intake) to 70 ng/l for a lifetime health advisory (HA) or "MCL" for this target population. (Delaware Riverkeeper Network)

COMMENT: *In considering these data, USEPA cautioned that "lack of human dosing information . . . precludes the use of these [human] immunotoxicity data in setting the [reference dose]."* (American Chemistry Council)

RESPONSE: The Health Effects Subcommittee acknowledges the significance of the studies of PFOS and decreased vaccine response. Additionally, the Subcommittee 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 quantitative basis for risk assessment. While the evidence for association of PFOS and decreased vaccine response in humans is strong, the Subcommittee maintains that the epidemiologic database is insufficient to support the use of this endpoint as the basis for quantitative risk assessment of PFOS. 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. As discussed in the detailed response to the next comment (6.) below, it remains unclear that the effects of PFOS can be separated from the effects of PFOA and other PFAS. Although the database for antibody response following vaccination is currently not conclusive enough to use as the primary basis for quantitative risk assessment, it clearly 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 PFOS and decreased response to vaccinations, including appropriate dose-response data, then this endpoint could be reconsidered for use as the basis for quantitative risk assessment.

6. Dose-response for decreased vaccine response for PFOS independent of co-occurring PFCs/PFAS

COMMENT:

- *We have recently showed that mutual adjustment of PFOA and PFOS results only in minor changes of the results, thus suggesting that, while humans are exposed to both compounds, PFOA immunotoxicity cannot explain the immunotoxic effects associated with PFOS, and vice versa. Likewise adjustment for the elevated PCB exposures in the Faroes did not materially affect the calculations.*

  > *The plot of the left [not reproduced here] shows the correlation between the age-5 serum-PFOS concentrations and the age-7 anti-diptheria antibody concentration in the birth cohort described in the JAMA article.*

  These findings support the notion that PFOS has an independent immunotoxic effect, which is in accordance with the data from the animal experiments referred to above and reviewed by NTP. Still, the human evidence reviewed relies on serum-PFOS measured at two postnatal ages, thus not taking into account the possible effects of immunotoxicity occurring during potentially more vulnerable ages in early postnatal life (i.e. infancy). The reported associations may therefore underestimate the toxicity at younger ages. In our most recent study of a younger Faroese birth cohort, we modeled serum-PFOS concentrations during infancy from the prenatal exposure level and information on the duration of breastfeeding. In the absence of blood samples, this calculation provides a reasonable estimate of the changing exposures. Our results showed a clear tendency that serum-PFOS at age 3 months was a much stronger indicator of vaccine antibody concentrations at age 5 years than was the calculated PFOS concentration at ages 6 to 12 months. Again, these results are crucial for prudent risk assessment, as they refer to vulnerable human populations and to exposure setting that are not easily modeled in laboratory animal studies. (Philippe Grandjean)

- *As a true threshold may not necessarily be present, the U.S. EPA relies on the calculation of the mathematically-defined benchmark dose level (BMDL) as a basis for deriving a reference dose (RfD) that is assumed to be virtually safe. As a default, the RfD is calculated as one-tenth of the BMDL, given that the BMDL is not a threshold and refers to an average degree of vulnerability. (When the RfD is expressed in terms of the serum concentration, it is sometimes called the Target Human Serum Level). Dealing with human populations where an unexposed control group is not present, we have used the recommended statistical method to calculate a BMDL for the serum-PFOS concentration as a predictor of immune deficiency. Using a default linear dose-effect curve and a benchmark response of 5% (meaning 5% decreases in the antibody level), we found the BMDL to be approximately 1.3 ng/mL. Modeling other curve shapes is possible; a logarithmic curve shape fits the data better and results in a lower BMDL. Analysis of pooled data may result in higher BMDL results due to the decreased uncertainty at a*

larger number of observations. The calculated BMDL should therefore be considered an approximate level. Assuming that this calculation reflects the PFOS effects only, as our most recent calculations suggest, the EPA guidelines indicate that an RfD can be estimated as one-tenth of the BMDL, i.e., 0.13 ng/ML, as a virtually safe level resulting from all PFOS exposure sources. It is my opinion, as based on my experience and expertise, that a safe water-PFOS limit must secure that human serum-PFOS levels are kept below this Target Human Serum Level. I note that the DWQI report has calculated a Target Human Serum Level of 23 ng/mL from animal toxicology studies. This very substantial difference clearly reflects that the DWQI relies on experimental studies using animals that are much more resistant to PFOS than humans, where exposures do not reflect he most vulnerable developmental window, and where the outcomes chosen do not properly reflect the adverse effects that are of critical importance in humans.

From the Target Human Serum level derived from animal studies, the DWQI Report recommends a water-PFOS limit of 12 ng/L. Considering the fact that this level is approximately 175-fold greater than the level calculated from human studies, a protective water limit would then be about 0.07 ng/L).

We have previously highlighted the fact that current limits for PFASs in drinking water greatly exceed our estimate of the concentrations necessary to prevent PFAS-associated immunotoxicity. The calculations above are not meant to constitute the exact calculations to be used in a formal risk assessment document, but the approximate magnitude of the epidemiology-based RfD illustrates the consequence of ignoring human data on PFOS associated adverse effects. (Philippe Grandjean)

- *From its review of the human evidence, which includes several other studies in addition to ours, the NTP concluded that PFOS is "presumed to be an immune hazard to humans…" while taking into regard a "moderate level of evidence from studies in humans." This conclusion refers to the fact that exposures to PFOS often correlate with exposures to other PFASs, so that epidemiological studies, in contrast to experimental studies, cannot easily attribute associations to particular PFASs. Nonetheless, as indicated above, limited human evidence is available on the adverse effects of PFOS alone, as most exposures involved PFAS mixtures that include PFOS* (Philippe Grandjean)

RESPONSE: As mentioned above, the Health Effects Subcommittee agrees that, all other factors being equal, high quality human dose-response data are preferable to animal data for human health risk assessment. The recent Budtz-Jorgensen and Grandjean (2017) analysis presented by the commenter suggests that a Target Human Serum Level based on human data for decreased vaccine response could be lower than the Health

Effects Subcommittee's Target Human Serum Level based on Dong et al (2009). However, the Subcommittee has several reservations about use of these data as the quantitative basis for a Reference Dose and Health-based MCL. As noted by the commenter, it is difficult to attribute effects observed in human studies to a single PFC such as PFOS, and the information available on epidemiological effects of PFOS alone is limited. Budtz-Jorgensen and Grandjean (2017) present PFOS BMDLs derived by adjusting PFC serum concentrations for the co-occurrence of PFOA, and thus, potentially provide a BMDL for relatively pure PFOS exposure (i.e. lower exposures to other PFCs could potentially still confound the PFOS relationship). However, it is not clear that the substantial co-exposures of PFOS and PFOA can be effectively separated by statistical means; the relatively small differences between adjusted and non-adjusted BMDLs support this concern. Relevant to this issue, it is noted that the Budtz-Jorgensen and Grandjean (2017) report is not a peer-reviewed paper and that the earlier published analysis of the same data (Grandjean and Budtz-Jorgensen, 2013) states that the contributions of PFOS and PFOA could not be statistically separated. Also relevant is the fact that the Faroe Islands data set analyzed in Budtz-Jorgensen and Grandjean (2017) is the only human PFC data set for which BMD analysis (including controlling for other PFC exposures) has been reported; it does not appear that such analyses will be available from other studies of human vaccine response and PFC exposure. In contrast, multiple animal data sets for immunosuppression by PFOS are available for comparative dose-response analysis.

PROTECTIVENESS OF RECOMMENDED HEALTH-BASED MCL

COMMENT: *Of concern is that the proposed MCL is not entirely health protective and that any additional exposure in drinking water may pose additional risk. According to the DWQI:*

> *It cannot be definitively concluded that lifetime exposure at the proposed Target Human Serum level is protective for the most sensitive effects, including in sensitive subpopulations.*

In 2016 the German Environment Agency completed a review of the evidence of harm from PFOS exposure and set a maximum blood plasma concentration of 5 ng PFOS/ml as the value at which adverse health effects are not expected. This health-protective value was based on human epidemiological evidence of harm, as well as animal studies indicating association of PFOA/PFOS exposure effects on fertility and pregnancy, weight of newborns at birth, lipid metabolism, immunity after vaccination and immunological development, hormonal development, thyroid metabolism and the onset of menopause. A health-protective value of 5 ng/ml is at the median value of the NHANES 2013-2014

testing as presented in the DQWI analysis. Any additional exposure through water would increase exposure over this threshold and should be avoided. From the DWQI analysis, the recommended value of 13 ng/L would lead to an additional exposure burden approximately 50% over the level expected to not cause adverse health effects, as summarized by the German Human Biomonitoring Commission." (Environmental Working Group)

RESPONSE: The Health Effects Subcommittee agrees that ongoing exposure to the recommended Health-based MCL of 13 ng/L is expected to increase serum PFOS levels, on average, by about 2.6 ng/ml (ppb) with average daily water consumption. The Subcommittee also agrees that epidemiological associations with health effects have been reported at serum PFOS exposures lower than those resulting from exposure to13 ng/L in drinking water. As mentioned by the commenter, there is uncertainty regarding the extent of protectiveness provided by the Health-based MCL. However, as discussed below, the epidemiological data for PFOS, including dose-response relationships, is currently not conclusive enough to use as the primary basis for risk assessment. That being said, evidence for associations of low exposures to PFOS with human health effects clearly supports the need for a protective approach in the risk assessment based on animal data.

ADDITIVE TOXICITY OF PFOS AND OTHER PFCs

COMMENT: *Alternatively, due to PFOS and PFOA co-occurrence in water supplies and additivity concerns, we recommend that the combination of PFOS and PFOA concentrations in water supplies be no higher than 13 ng/L. [PFOA + PFOS] ≤ 13 ng/L* (Delaware Riverkeeper Network)

COMMENT: *The DWQI should also consider the additive nature of toxicity from PFOS and other PFC compounds found in NJ water supplies to set a comprehensive MCL for the sum concentration of this family of chemical contaminants."* (Environmental Working Group)

COMMENT: *The DWQI should evaluate and set an MCL based on the combined concentration of PFC chemicals in drinking water*

It is very encouraging that the DWQI and the state of New Jersey are moving forward on establishing contamination limits for PFOA, PFOS and PFNA in drinking water. In the DWQI analysis, it was explicitly stated that the same epidemiology studies of health impacts associated with PFOS exposure are also associated with PFOA exposure:

Additionally, the health effects associated with PFOS in epidemiology studies are also associated with PFOA. Therefore, the toxicity of PFOS and other PFCs may be additive. Although PFOS and other PFCs, including PFOA, are known to cooccur in some NJ public water supplies, the potential for additive toxicity of PFOS and other PFCs was not considered in development of the Health-based MCL.

Setting MCLs for these contaminants individually is an important first step, but the combined exposure to PFCs must be considered in order to protect health. The EPA established a precedent for this approach by setting a health advisory for combined PFOA and PFOS exposure. These chemicals, along with other PFCs, often contaminate the same water sources. While New Jersey has done water testing with lower reporting limits than the EPA through the UCMR program, it is possible – if not likely – that other PFCs, including short chain replacement chemicals, are contaminating drinking water in the state and adding to the combined toxicity (Environmental Working Group)

RESPONSE: The potential for additive toxicity of PFOS and other PFCs is acknowledged in the Uncertainties section of the Health-based MCL Support Document (p. 277). However, as discussed in the Health-based MCL Support Document, the toxicological effects and mode of action of PFOS differ in some respects from PFOA and PFNA, the other PFCs evaluated by the DWQI. Additionally, because the dose-response for some effects is steepest at low exposures and approaches a plateau at higher exposures, dose-response for mixtures may be complex and dose-dependent (Post et al., 2017). Although cumulative effects were not considered in developing the Health-based MCL, an important benefit of addressing exceedances of the Health-based MCL is that treatment removal processes intended to remove the PFOS may also partially or totally remove other types of PFCs, other types of per- and polyfluoralkyl substance (PFAS), and other unrelated contaminants that may be present at levels of public health concern (Post et al., 2017).

COMMENTS ON "RUTGERS PILOT STUDY OF PERFLUOROCHEMICAL COMPOUNDS IN PAULSBORO RESIDENTS, PRELIMINARY STUDY REPORT" (Chemistry Council of New Jersey)

COMMENTS:

- *CCNJ/SRIN strongly urge that the report entitled Rutgers Pilot Study of Perfluorochemical Compounds in Paulsboro Residents, Sept. 13, 2017, and the underlying data gathered by Rutgers upon which it is based, be evaluated by DWQI and NJDEP, as the data would allow a direct assessment of some of the key assumptions made by DWQI regarding the association between PFC drinking water concentrations and blood serum levels.*

- *CCNJ/SRIN and our members continue to advocate for DWQI's and NJDEP's transparent and thorough consideration of the Rutgers Pilot Study of Perfluorochemical Compounds in*

Paulsboro Residents, Sept. 13, 2017 (Attachment 1), and the underlying Perfluorinated Compound (PFC) blood sampling data from Paulsboro.

The data gathered by Rutgers is the only available scientifically-gathered evidence of PFC blood serum levels in residents who consumed water from municipal wells affected by Perfluorononanoic Acid (PFNA), and one of the few paired data sets for Perfluorooctanoic Acid (PFOA) or PFOS. To date, DWQI has not acknowledged that these data exist. Ignoring these data undermines the credibility of DWQI's PFC recommendations. The Paulsboro data are readily available, reliable, recent and local, and directly relevant to DWQI's recommendations, including for PFOS, which was detected in both the Paulsboro water supply and in residents' blood serum. CCNJ/SRIN urge DWQI to include these data in its regulatory consideration/calculation.

The more than 1,000-page report by the DWQI Health Effects Subcommittee, which includes more than 30 pages of references alone, does not mention Paulsboro or the fact that more than 1,000 residents of Paulsboro had their blood sampled for PFCs, including PFNA, PFOA, and PFOS, in 2016. Nor does it mention that Rutgers enrolled 181 Paulsboro residents in a study and, in cooperation with Rutgers, those residents shared their blood serum results and information about their use of the Paulsboro water system with the Rutgers research team. Additionally, a large subset, 116 residents, answered detailed questions for Rutgers, including water consumption information and health conditions that may be associated with PFCs.

RESPONSE: Several points in this comment need to be addressed. First, a member of the Health Effects Subcommittee has discussed this study with the Rutgers researchers and has shared this information with the Subcommittee. The Rutgers researchers stated that this study was not intended to, and cannot, provide information on the quantitative relationship between drinking water exposure to PFCs (i.e. PFNA, PFOA, or PFOS) and serum PFC levels. The Subcommittee agrees with this conclusion. Second, the relevance of this study to the PFOS risk assessment is even more unclear, since levels of PFOS in Paulsboro drinking water were relatively low (i.e. 3 to 12 ng/L), while PFNA and PFOA levels were much higher. Finally, the report cited by the commenter is a brief preliminary report, written in layperson's language, that was shared with study participants at a public meeting. It is not a full scientific report, and it does not include complete information about the study's methodology, results, and conclusions.

COMMENT:

- *Based on the existence of a questionnaire that was formally developed and approved by Rutgers (Attachment 2), we believe that water consumption data was collected during the Paulsboro study. This questionnaire includes very specific questions about water consumption; please see excerpt below:*

SECTION 3
The next questions are about the time BEFORE you knew about the PFNA in the drinking water and BEFORE you or the borough of Paulsboro took steps to reduce your PFNA exposure.

During the time that you lived in a home served by Paulsboro public water supply, and BEFORE you knew about the PFNA in the drinking water, about how many 8 oz cups of tap water or beverages prepared with tap water did you usually drink per day?

Note: 1 Gallon (128 oz.) = 16 cups; 1 quart (32 oz.) = 4 cups; 1 pint (16 oz.) = 2 cups

_____ *Cups per day*

According to the final, published Rutgers report, 116 long form surveys were completed by Paulsboro residents, so it appears that very direct questions were asked of residents and collected by Rutgers about water consumption.

Rutgers published and provided to the residents a report that analyzed those 181 blood serum results. That report, entitled Rutgers Pilot Study of Perfluorochemical Compounds in Paulsboro Residents, Sept. 13, 2017, and the underlying data gathered by Rutgers upon which it is based, should be evaluated as part of DWQI and NJDEP regulatory considerations for PFCs, as the data would allow a direct assessment of some of the key assumptions made by DWQI regarding the association between PFC drinking water concentrations and blood serum levels. In addition to the detailed information collected on a subset of the residents, Paulsboro itself has records of when it used its various wells to supply its residents with drinking water and, therefore, there exists a basis for understanding residents' drinking water exposures and associated PFC blood serum levels. However, in the event that Rutgers ultimately did not collect the water consumption data, CCNJ/SRIN would like an explanation as to why not given its direct relevance to the study. In terms of advancing the science, if this data was collected, it would be far more useful for the data's existence to be publicly acknowledged and an explanation given by Rutgers and the State regarding why they are not taking the logical next step to evaluate it.

RESPONSE: First, as above, the Rutgers study collected data from residents of a community exposed to elevated levels of PFNA in their drinking water, and therefore it does not appear to

be relevant to risk assessment of PFOS in drinking water. Second, as above, the Rutgers researchers and the Subcommittee are in agreement that the study will not provide useful quantitative information on the relationship between drinking water exposure and serum levels of PFCs in general for several reasons, including because the participants' historical exposure to PFCs in drinking water will remain undetermined. Multiple wells with different PFC levels over time supplied drinking water to different parts of Paulsboro, and the mixture of wells supplying water to any given location varied over time. Third, the preliminary study report does not mention that the survey asked about drinking water consumption and does not discuss the relationship of drinking water consumption to serum PFC levels. Furthermore, the full history of the PFC concentrations in individual wells over time is not known and the time at which different individuals began to receive PFNA-contaminated water is not known.

COMMENTS*:*

- *In addition, we understand that it is possible that there were data quality issues. Yet, this would be puzzling given that Rutgers did use information obtained from other questions in the same survey, for example to help group results by age and sex. If New Jersey is going to be the first in the United States to regulate far and beyond the United States Environmental Protection Agency (USEPA)'s standards, then the data puts researchers in a unique position to support such an action. They can examine available data from the surveys and water sample results to provide some clarity to assumptions that DWQI and NJDEP are relying upon in their calculations. This can also advance the scientific understanding for PFNA, PFOA, and PFOS, in general.*

- *The Paulsboro study is relevant to DWQI's PFOS MCL recommendation because it includes measurements of multiple PFCs, including PFOA and PFOS. If the assumption is that human health effects of PFNA, PFOA, and PFOS are driven by concentrations in our bodies, the link between external exposure through drinking water and someone's internal dose needs to be calculated with extreme rigor.*

- *On the sample design itself, CCNJ/SRIN agree that the data were not collected in a scientifically rigorous way. However, the data still provide important information, not the least of which would be a check on whether the assumptions adopted by DWQI and NJDEP are consistent with data for each of the PFCs (PFNA, PFOA, and PFOS) for this specific sample. For example, Rutgers could examine data on serum and water levels to determine if individuals with elevated serum levels (higher than NHANES) also have higher exposures based on the reported water consumption rates and the concentrations in water (compared to the proposed MCL).*

  The Paulsboro dataset may prove useful to explore many of the assumptions made for PFNA, PFOA, and PFOS. There should be a transparent discussion of its strengths and weaknesses.

RESPONSE: As above, the relevance of this study to the PFOS risk assessment is unclear, since levels of PFOS in Paulsboro drinking water were relatively low (i.e. 3 to 12 ng/L) and varied over time and at different locations within the system. As mentioned by the commenter, estimation of a serum to water ratio requires detailed exposure history, which is unavailable in this study. As such, the Rutgers researchers stated that this study was not intended to, and cannot, provide information on the quantitative relationship between drinking water exposure to PFCs (i.e. PFNA, PFOA, or PFOS) and serum PFC levels. The Subcommittee agrees with this conclusion.

COMMENT: *For example, for PFNA, the DWQI MCL recommendation is based on the assumption that 4.9 parts per billion (ppb) of PFNA in human blood is an appropriate protective target serum level. However, according to Rutgers, the measured mean level of PFNA in the blood of 181 Paulsboro residents is 3.6 ppb. In other words, the actual data are below the target level that NJDEP and DWQI have determined is protective. And, yet, Paulsboro drinking water well No. 7 had measured levels of PFNA near 100 ppt or more in August of 2009 and in October 2013 through when the well was taken offline in April 2014. This concentration of PFNA in drinking water is over 7 times higher than the recommended MCL; however, the residential blood serum data shows that serum PFNA levels did not exceed DWQI's target human blood level.*

The concentrations of PFNA, PFOA, and PFOS in blood serum of almost 200 residents in Paulsboro have been accurately measured. If 100 ppt in drinking water did not cause the average level in blood serum to exceed the level DWQI and NJDEP used to calculate the MCL, then why would NJDEP and DWQI insist that water suppliers across the state must test for PFNA down to 2 ppt, and install expensive treatment to keep the level of PFNA in their water supplies below 13 ppt?

RESPONSE: This comment is not relevant to the Health-based MCL for PFOS, since it discusses PFNA rather than PFOS. However, as above, both the Rutgers researchers and the Health Effects Subcommittee conclude that this study is not useful in providing quantitative information on the relationship between drinking water exposure and serum levels of PFCs, including PFNA, for several reasons including because the participants' historical exposure to PFCs in drinking water will remain undetermined.

COMMENT: *There are simply not that many datasets available that provide this information. This is a study of approximately 200 individuals, each of whom provides a direct measure of the same variable that NJDEP is trying to estimate. By comparison, in terms of sample size alone, this study is four times the size of the one and only study in humans NJDEP and DWQI relied upon to support their estimate of the half-life of PFNA in serum; that study*

only had 50 participants. NJDEP defended its position to use that study in its public response-to-comments, indicating that they were confident such information would support a central tendency estimate of the serum:water ratio. Why not take the next step to evaluate this study?

RESPONSE: As above, the Rutgers researchers and the Health Effects Subcommittee agree that this study does not provide quantitative data on the relationship between PFCs in drinking water and serum PFC levels. Additionally, while not relevant to the Health-based MCL for PFOS, it is incorrect that NJDEP and DWQI relied on only one study with 50 participants to estimate the human half-life of PFNA. As discussed in the Health-based MCL Support Document for PFNA (http://www.nj.gov/dep/watersupply/pdf/pfna-health-effects.pdf), the PFNA half-life was estimated based on multiple human and animal studies of the toxicokinetics of PFNA and PFOA.

COMMENT: *DWQI and NJDEP rely heavily on their assumptions about how PFCs are retained in human blood (versus actual data) to recommend MCLs as extremely low and unprecedented as 13 parts per trillion (ppt) for PFNA and PFOS and 14 ppt for PFOA. These levels are far lower than guidance from USEPA without scientific justification or evidence. Importantly, the levels do not appear defensible when compared to actual empirical data.*

RESPONSE: The human half-life values used in developing the PFOS and PFOA Health-based MCLs are based on empirical data on the decline in human serum levels over time after exposure ended. Specifically, the USEPA clearance factor used in the development of the Health-based MCL recommendation for PFOS utilized data on measured half-life from Olsen et al. (2007). Olsen et al. (2007) provides a reliable measure of half-life in humans from a retired worker population followed for 5 years. The USEPA (2016) Health Advisories for PFOS (and PFOA) use the same half-live values as the DWQI Health-based MCLs. As such, the differences between the DWQI Health-based MCLs and the USEPA Health Advisories arise from factors other than the use of different half-lives, such as the DWQI's consideration of more sensitive toxicological effects.

COMMENT: *In addition, we advocate consideration of the study and the underlying data because:*

1. The data are reliable. Phlebotomists were used to gather the samples and a New Jersey certified lab was used to analyze them. Rutgers itself relies on the data in issuing its report.

2. They are the only available empirical data involving measured quantities of PFCs in drinking water and in human blood serum of New Jersey system users.

3. More than 1,000 Paulsboro residents chose to have their blood serum levels sampled for PFCs and 181 of that group chose to make the results available to Rutgers, in response to its request. No one claims that this is a random sampled population necessary for a health study, but it is false to suggest that this data could have no scientific value as to the very assumptions, especially the serum:drinking water ratio, that DWQI has made in their proposed MCLs for several PFCs.

Scientists are trained and able to recognize and evaluate sample size and selection bias, as well as time of exposure versus time of sampling, and use empirical data for appropriate purposes. In this case, valid, directly relevant data are available to compare to assumptions being relied on by DWQI and NJDEP to the PFCs actually detected in New Jersey residents using affected water. The residents of Paulsboro and all New Jerseyans deserve a straightforward discussion and consideration of the Paulsboro residents' blood results. (Chemistry Council of NJ)

RESPONSE: Some of the points in this comment were addressed in other responses above. The fact that phlebotomists and a certified lab were used does not impact the relevance of the data for evaluating the quantitative relationship between PFCs in drinking water and serum.

As stated above, this study does not provide quantitative data on the relationship between PFCs in drinking water and serum PFC levels that can be used in Health-based MCL development. This is in contrast to other studies that provide estimates of this relationship from reliable historical data on household concentrations of PFCs in drinking water over time, or half-life estimates based on empirical data on decline in serum PFC concentrations after exposure ended. Additionally, as the commenter has stated, the non-random "study" selection may have resulted in a bias such that individuals with higher (or lower) PFC serum levels are more or less likely to participate in the survey and are not representative of community exposure.

RESPONSE SUMMARY:
The preliminary report on the Rutgers study does not make any statements about the quantitative relationship between drinking water exposure and serum levels. In summary, the Rutgers researchers state that this study does not provide quantitative data on the relationship between PFCs in drinking water and serum PFC levels that can be used in Health-based MCL development, and the Health Effects Subcommittee agrees with this conclusion.