HEALTH-BASED MAXIMUM CONTAMINANT LEVEL SUPPORT DOCUMENT: PERFLUOROOCTANOIC ACID (PFOA) RESPONSE TO PUBLIC COMMENTS

New Jersey Drinking Water Quality Institute
Health Effects Subcommittee

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Background

- Health Effects Subcommittee presented draft Health-based MCL document on September 22, 2016
- Document was posted for public comment, and written comments were accepted until November 21, 2016
- Ten submissions include comments relevant to Health Effects Subcommittee documents
  - Two support the Health-based MCL
  - Five suggest lower Health-based MCL
  - Two suggest higher Health-based MCL
  - One discusses only DWQI review of USEPA Health Advisory and did not comment on Health-based MCL

Background (*continued*)

- All comments were considered and responded to by Health Effects Subcommittee
- Summary of comments are presented here. Detailed response to comments will be posted online
- All comments will be linked from response document
- Health-based MCL Support Document includes minor revisions including additional citations and wording clarifications

General Comments

- **Comment**: General support of approach used to develop Health-based MCL
  - **Response:** Comments are acknowledged
- **Comment**: Consideration of additional references
  - **Response:** Additional references recommended by commenters were reviewed and some citations added
- **Comment:** Unlike USEPA and others, DWQI does not recognize lack of evidence and uncertainties regarding health effects of PFOA
  - **Response:** DWQI recognizes uncertainties associated with risk assessment in general and specifically for PFOA
  - PFOA has more health effects information than many other drinking water contaminants evaluated by DWQI which reduces the uncertainty in the risk assessment

General Comments *(continued)*

- **Comment**: Selectively overemphasized data which supports conclusions and downplayed studies/results that did not support conclusions
  - **Response:** Detailed individual study and summary tables for human and animal studies are presented
  - For human endpoints selected for review, complete epidemiologic database was evaluated regardless of positive or negative associations
  - For toxicological endpoints reviewed in depth, potential reasons for differing results among studies are discussed
- **Comment**: "Despite evidence to the contrary, DWQI classifies PFOA as a developmental toxicant." This contributes to "unwarranted concern" about risks for women of childbearing age and infants
  - **Response:** PFOA is a well-established developmental toxicant. It caused numerous developmental effects in animal studies and is associated with decreased fetal growth in humans
  - USEPA Drinking Water Health Advisory for PFOA is based on developmental effects, and USEPA considers pregnant/lactating women and infants to be susceptible subpopulations for PFOA's effects

General Comments *(continued)*

- **Comments:** USEPA Health Advisory is higher than DWQI Health-based MCL. DWQI does not explain why USEPA Health Advisory is “defective” or why a lower value is necessary
  - A thorough review of the basis of the USEPA Health Advisory is presented in Appendix 2 of the document. The Health Effects Subcommittee concluded that USEPA Health Advisory is not sufficiently protective

Margin of Exposure

- **Comment:** Consider appropriateness of "margin of safety" (MOE) approach for PFOA used in Health Canada (2012). Health Canada (2012) did not find it necessary to apply additional "uncertainty factors"

  Response:

  - Health Canada (2012) is not relevant to development of human health value for PFOA in drinking water
  - Instead supports decision on whether PFOA meets criteria for listing as harmful under Canadian Environmental Protection Act (CEPA, 1999)
    - CEPA is related to use of PFOA in products and is analogous to USEPA TSCA
  - In contrast, Health Canada (2016) developed drinking water Maximum Acceptable Concentration using uncertainty factor approach

Significance of Increases in Human Serum PFOA from Drinking Water

- **Comment**: Uncertainty and variability in underlying assumptions should be discussed. Actual risks should be tied to PFOA serum levels
  - **Response:** Document discusses inter-individual variability in PFOA serum levels from a given drinking water concentration
  - Human health endpoints associated with serum PFOA levels that result from drinking water exposure are discussed in document
- **Comment**: Serum levels below Target Human Serum level but above background levels present a *de minimis* risk. Furthermore no specific health risk statements can be made for levels above the Target Human Serum level
  - **Response:** Serum PFOA levels, both below and above the Target Human Serum level, are associated with health endpoints in the general population and communities with contaminated drinking water
  - It can not be definitively concluded that lifetime exposure to PFOA in drinking water at concentrations such as the recommended MCL are protective of sensitive subpopulations with a margin of exposure

Development of Reference Dose

- **Comment:** Justification is needed for selection of non-cancer endpoints, including discussion of adversity
  - **Response:** Non-cancer endpoints used for quantitative evaluation are thoroughly discussed, including their adversity and suitability for use in risk assessment. Details are presented in tables and text
- **Comment:** Document states that the non-cancer endpoints reviewed yielded relatively consistent points of departure
  - **Response:** This comment is not accurate
  - Of the toxicological endpoints with data for dose-response modeling, delayed mammary gland development is the most sensitive, and hepatic toxicity (as indicated by increased liver weight) is the next most sensitive. Other endpoints (e.g. immunotoxicity) with dose-response data are less sensitive

Development of Reference Dose - Increased Liver Weight

- **Comment:** Increased liver weight, in the absence of histopathological changes indicative of cell damage, at the same dose in the same study, should be considered non-adverse
- **Comment:** At the low dose used as the point of departure by DWQI, increased liver weights is an adaptive rather than adverse response associated with normal liver functioning. Liver size alone is not a reliable indicator of hepatic toxicity
  - **Response:** "…. numerous studies of PFOA have demonstrated that increased liver weight co-occurs with and/or progresses to more severe hepatic effects including increased serum liver enzymes, hepatocellular necrosis, fatty liver, and/or hyperplastic nodules. Additionally, recent studies show that cellular damage indicative of liver toxicity persists until adulthood following developmental exposure to PFOA."
  - Several PFOA risk assessments recommended by the commenter, including Health Canada (2016) and enHealth (2016), are based on increased liver weight

Development of Reference Dose – Use of Rodent Toxicity Data

- **Comment:** Use of rodent data is inconsistent with ATSDR (2015) and others. It is well known that PFOA mediates its effects through PPAR-alpha and other receptors for which humans are less responsive than rodents.
  - **Response:** Detailed evaluation of primary data in DWQI mode of action analysis supports use of rodent studies
  - Joint NJDEP/NJDOH comments on ATSDR (2015), which is a draft, note its general deficiencies and, specifically, that its decision to dismiss rodent data "does not appear to be scientifically supportable."
  - Dose-response curves for hepatic toxicity and PPAR-alpha activation for PFOA are similar in non-human primates and rodents
  - PFOA causes hepatic toxicity in PPAR-alpha null mice, in some cases more severe than in wild type mice
  - Increased liver weight does not correlate with PPAR-alpha activity in standard rodent strains
  - Developmental and immune system toxicity effects mediated by PPAR-alpha are not known to be less sensitive in humans than rodents.

Development of Reference Dose – Mammary Gland Developmental Effects

- **Comment:** Delayed mammary gland developmental should be used as primary basis for risk assessment. The resulting Health-based MCL would be 1 ng/L or less
  - **Response:** Although it is well established that PFOA causes this effect in mice, there is no precedent for delayed mammary gland development as the primary basis for risk assessment
  - Permanent histopathological changes in adulthood were observed, but were evaluated in only one study
  - There is limited toxicological data on lactational function
  - More appropriate to consider this effect with additional uncertainty factor
  - If additional future studies provide further support for these findings, use of this endpoint as primary basis for Health-based MCL could be reconsidered

Development of Reference Dose – Mammary Gland Developmental Effects *(continued)*

- **Comment:** Inconsistencies among studies of this effect (inhibition, no effect, stimulation) should be considered. Delayed mammary gland development may not be biologically significant because adverse effects on nutritional support of offspring have not been demonstrated
  - **Response:** All studies of mammary gland development were reviewed in detail, including potential reasons for differing results among studies
  - Nine studies of prenatal/early life exposure found delayed mammary gland development; the only negative study had problematic issues.
  - Studies of peripubertal exposure are not comparable to prenatal/early life exposure studies because effects on mammary gland development are dependent on lifestage
  - Effects on structure of an organ are considered adverse. Structural changes from developmental exposure persisted until adulthood.
  - Available information is insufficient to make conclusions about toxicological effects on lactational function
  - Three human studies found associations of maternal PFOA exposure and shorter duration of breastfeeding

Development of Reference Dose – Mammary Gland Developmental Effects *(continued)*

- **Comment:** Individual studies on mammary gland developmental delays often had significant weaknesses, such as lack of statistical adverse effects "due to interindividual variance and multiple criteria used to calculate mammary gland development scores"
  - **Response:** The quote is incorrectly attributed and used out of context
  - The intent of the quote was not to say that individual studies of this effect often had significant weaknesses. Instead, it refers to one statistically insignificant data point in one study

Development of Reference Dose – Selection of Uncertainty Factors

- **Comment:** UF of 10 for low-dose developmental effects is not used in PFOA risk assessments developed by other jurisdictions
  - **Response:** This UF is used in Maximum Exposure Guideline for PFOA in drinking water developed by Maine Department of Health and Human Services (2014)
- **Comment:** DWQI PFOA MCL of 14 ppt is lower than federal 70 ppt guideline because of addition of arbitrary "safety factor"
  - **Response:** Inclusion of UF is not arbitrary, but is based on USEPA risk assessment guidance: UF should be used "*if there is concern that future studies may identify a more sensitive effect, target organ, population, or lifestage*."
- **Comment:** Evidence for use of UF of 10 for potential low-dose developmental toxicity is weak
  - **Response:** Delayed mammary gland development at low doses in mice is well-established
  - Low-dose developmental effects also include persistent liver toxicity
  - Additional UF is needed to protect for these low dose developmental effects

Cancer Risk Assessment

- **Comment:** Uncertainties and limitations in quantitative cancer analysis should be thoroughly discussed
  - **Response:** Uncertainties about both human relevance of effects seen in animals and extrapolation from higher tumor incidence in animal studies to one-in-one million cancer risk levels are inherent to all cancer risk assessments based on animal data
  - For PFOA, uncertainty is reduced by human-to-animal comparison based on internal dose, rather than administered dose

Cancer Risk Assessment Carcinogenicity Classification

- **Comment:** Link between PFOA exposure and carcinogenicity in humans is overstated…only positive studies summarized and conflicting evidence ignored
  - **Response:** Quantitative cancer risk assessment is based on animal tumor data, not human data
  - Conclusion of causality in humans is not required for quantitative cancer risk assessment
  - DWQI did not independently develop a carcinogenicity descriptor
  - USEPA Science Advisory Board, USEPA Office of Water, and IARC conclusions that PFOA is likely, suggestive, or possible carcinogen, along with DWQI mode of action evaluation for rat tumors, support cancer potency factor approach
  - Both positive and negative studies relevant to these classifications are summarized
- **Comment:** IARC classification has shortcomings while Health Council of Netherlands was not considered
  - **Response:** Health Council of the Netherlands relies on IARC assessments when possible, but it evaluated PFOA in 2013 prior to IARC (2016) PFOA evaluation
  - Health Council of Netherlands criteria for carcinogenicity classification differ from those used by USEPA, NJDEP, and DWQI

Cancer Risk Assessment Carcinogenicity Classification *(continued)*

- **Comment:** Outdated and unofficial USEPA SAB (2006) conclusions are over highlighted while USEPA Office of Water (2016) diminished. SAB report is not peer-reviewed
  - **Response:** Both USEPA SAB (2006) and USEPA Office of Water (2016) conclusions are presented
  - SAB (2006) represents conclusions of a panel of scientists who served as peer reviewers to USEPA; therefore, SAB reports do not undergo further peer review
  - SAB (2006) is final and official

Cancer Risk Assessment Interspecies Extrapolation

- **Comment:** Human equivalent dose for cancer risk assessment is derived from an administered dose in rats. This is inconsistent with use of only studies with serum PFOA data for non-cancer Reference Doses
  - **Response:** Serum PFOA data are not reported in study that provides tumor data
  - Animal-to-human comparisons were based on internal dose using ratio of human-to-animal half-lives
  - Ratio of half-lives is a valid approach and has been used in other PFOA risk assessment including USEPA Provisional Health Advisory (2009)

Exposure Assumptions - Ingestion Rate

- **Comment:** Using adult default exposure values is inappropriate since does not protect children
  - **Response:** Higher exposures of infants and children from drinking water are acknowledged
  - Child exposure assumptions are not used because of toxicokinetic uncertainties. Exposure rates in infants and children vary over time, and durations are too short to reach steady state
  - Relative Source Contribution partially accounts for higher PFOA exposures in young infants

Exposure Assumptions - Relative Source Contribution

- **Comment:** Lorber and Egeghy (2011) determine RSC at 24%
  - **Response:** Acknowledged, RSC of 20% selected by DWQI
- **Comment:** Data presented by Lorber and Egeghy (2011) support RSC of 60-70%
  - **Response:** Commenter misunderstands data presented by Lorber and Egeghy (2011). As above, these data support RSC of 24%
- **Comment:** Sufficient information is available to derive chemical specific RSC. Default RSC of 20% is inconsistent with non-default RSC used in PFNA Health-based MCL
  - **Response:** There is no NJ-specific biomonitoring data for PFOA. PFOA occurrence in NJ drinking water much greater than national. Therefore, occurrence in other environmental media may also be greater, resulting in additional non-drinking water exposures in NJ
  - PFOA detected in drinking water at locations throughout NJ, and sources are largely unknown. In contrast, detections of PFNA in NJ are limited to vicinity of likely industrial source

Human Epidemiology

- **Comment:** Certain associations are likely to be causal in humans. Low doses are likely to be physiologically quite active, and no non-causal reasons for some consistent associations have been found
  - **Response:** Acknowledged. Document describes associations found at general population serum levels. The points made in the comment support the need for caution for additional exposure to PFOA from drinking water

Human Epidemiology
Selection of Immune Response Endpoint

- **Comment:** Recommend Health-based MCL of less than 1 ng/L based on human immunotoxic effects during early life, as calculated by Grandjean and Budtz-Jorgensen (2013) using data from Grandjean et al. (2012)
  - **Response:** Health Effects Subcommittee reevaluated Grandjean et al. (2012) and other human studies of immune response following vaccination
  - Grandjean et al. (2012) unable to mutually adjust for both PFOA and PFOS
  - Limited number of comparisons across the same vaccination types and lack of consistency across other human studies of immune response following vaccination
  - Grandjean et al. (2012) remains extremely valuable for hazard identification
  - If findings from future studies provide additional support, use of this endpoint for quantitative risk assessment could be considered

Human Epidemiology Clinical Trial Data

- **Comment:** Consider controlled phase I clinical trial of APFO (PFOA) as an anti-cancer treatment in 28 advanced cancer patients. At high levels, normal liver and kidney function were not affected
  - **Response:** This study is not a peer-reviewed publication. It is an abstract of a poster presentation
  - **Response:** Abstract reports that one patient experienced possible drug related toxicity consisting of “grade 5 renal failure and transaminitis [indicative of liver damage]”

Summary

- All comments were considered by Health Effects Subcommittee
- Complete comments and responses will be posted
- Responses to USEPA comments on DWQI review of USEPA Health Advisory (Appendix 2 of Health-based MCL document) are included in response document to be posted, although not presented here
- Draft Health-based MCL Support Document was revised where appropriate
- Revisions to draft document are minor, and conclusions did not change
- Health-based MCL recommendation remains unchanged at 14 ng/L