Health-based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS) 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 November 28, 2017
- Document was posted for public comment on December 5, 2017, and written comments were accepted until February 5, 2018.
- Six submission included comments relevant to Health Effects Subcommittee document
  - One supports the Health-based MCL
  - Three suggest lower Health-based MCL
  - Two suggest higher Health-based MCL

Background *(continued)*

- All comments were considered and responded to
- Summary of comments and responses are presented here
- Detailed responses and complete comments will be posted online
- Submitted comments will be linked from response document
- No substantive changes in final Health-based MCL Support Document - includes minor revisions including additional citations and wording clarifications.

Health-based MCL Support Document

- Based on decreased plaque forming cell response (PFCR) in mice (Dong et al., 2009)
  - Well established toxicological effect of PFOS – four positive studies and only one negative study.
    - Identified as sensitive and relevant endpoint in several other scientific evaluations of PFOS
  - Appropriate basis for risk assessment
    - Indicator of decreased immune function and potential disease risk
    - Used as basis for EPA IRIS risk assessments of other chemicals
  - Supported by epidemiological evidence for analogous effect in humans - decreased vaccine response
- Lowest of the potential Health-based MCLs for non-cancer effects
- **Recommended Health-based MCL is 13 ng/L**

General Comments

Comment: General support of approach used to develop Health-based MCL

- **Response:** Comments are acknowledged

Comment: Consideration of additional references

- **Response:** Health Effects Subcommittee thoroughly and objectively evaluated the relevant scientific information. Additional references relevant to immune effects of PFOS which Subcommittee has become aware have been added.

Comment: Consideration of other PFOS evaluations including: enHealth (2016), USEPA (2016) Health Advisory, and Health Canada

- **Response:** Subcommittee has reviewed these PFOS evaluations.
- enHealth (2016) guideline is outdated and not scientifically supportable. It is far higher than would be health protective.
- Health-based MCL document includes detailed review of USEPA Health Advisory and concludes that it is not sufficiently protective.
- Health Canada document is a draft and is subject to change based on comments received.

Significance of PFOS environmental contamination and drinking water exposure

Comment: Observed declines in human serum PFAS concentrations are due to active interventions to reduce consumer-product exposure. Improvement in serum PFAS does not extend to those who are exposed to contaminated drinking water.

- **Response:** Subcommittee agrees with comment. Continued exposure to PFOS in drinking water leads to elevated serum PFOS levels which remain elevated for many years after exposure ends.

Development of Reference Dose (RfD):
Use of immune toxicity/ decreased plaque forming cell response (PFCR)

Comment: Selection of immune system changes as the current most sensitive endpoint is scientifically defensible.

Comment: The effect of immunotoxicity has been well documented and may well represent the critical adverse effect in humans on which risk assessments should focus

- **Response:** Agree with commenter's support of use of immune system effects as basis of RfD

Comment: The choice of immunological effects as the critical effect is inconsistent with other regulatory agency reviews that have concluded that this endpoint requires further study

- **Response:** Subcommittee has reviewed PFOS risk assessments developed by other agencies. Endpoints selection varies: decreased offspring body weight in rats (USEPA, 2016), hepatocellular hypertrophy in rats (Health Canada, 2016), and increased liver weight in monkeys (ATSDR, 2015).
- NTP (2016) concluded: "PFOS is presumed to be an immune hazard in humans"

Development of Reference Dose (RfD):
Use of immune toxicity/ decreased plaque forming cell response (PFCR) - *continued*

Comment: Inconsistent immunosuppressive effects across studies
- **Response:** Only one of five PFOS studies evaluating PFCR in mice was negative
- USEPA (2016) HE Support Document for PFOS: "…consistent suppression of SRBC response [i.e. PFCR] in animals"

Comment: Questionable human relevance of the observations in mice
- **Response:** Decreased antibody response to vaccines is associated with PFOS in humans and is directly analogous. Human studies of this endpoint are presented in detail.

Comment: …findings may not represent an adverse effect
- **Response:** USEPA IRIS has used decreased PFCR as the basis for RfD for at least two other chemicals.

Comment: Epidemiological evidence in human are inconclusive
- **Response:** As reviewed in detail in the Health-based MCL Support Document, all but one of five relevant epidemiology studies found an association between PFOS and decreased antibody response to at least one vaccine. Furthermore, RfD is based on animal data, and it is not necessary to conclusively prove that this effect occurs in humans.

Development of Reference Dose (RfD):
Use of PFCR from Dong et al. (2009) as key endpoint/study

Comment: NTP (2016) systematic review of animal data concluded they cannot be confident in outcome assessment in Dong et al. (2009)

- **Response:** NTP rated outcome assessment as “probably high risk of bias” because Dong et al. (2009) did not report (as for most toxicology studies published in peer-reviewed journals) or later provide information to NTP about whether outcome assessors were blinded.
- NTP noted that “well-established methods” were used to measure PFCR in this study.
- Based on consideration of all relevant factors, NTP concluded there is high confidence that PFOS exposure is associated with suppression of the antibody response based on available animal studies.

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.

- **Response:** The intent of the comment is unclear. The non-monotonic response of NK cell activity is acknowledged, but this is not related to PFCR response which is the basis of Health-based MCL.

Development of Reference Dose (RfD):
Dong et al. (2009) vs. other toxicological studies of immune effects

Comment: Five studies investigated immune system effects in mice exposed to PFOS. Although multiple studies reported immune effects, USEPA concluded differences in levels at which effects were reported highlight the need for additional research to confirm NOAEL and LOAEL.

- **Response:** Health-based MCL Support Document discusses these differences among studies. Difference may reflect methodological differences between studies (e.g. dose selection, strain, source of SRBCs).
- Study selected as basis for RfD was not the most or the least sensitive of the four studies showing this effect.
- Database clearly demonstrates a consistent observation that PFOS causes decreased PFCR.

Development of Reference Dose (RfD):
Dong et al. (2009) vs. other toxicological studies of immune effects - *continued*

Comment: Subsequent Dong et al. (2011) study conflicts with Dong et al. (2009)

- **Response:** This comment is misleading since studies measured different endpoints following SRBC inoculation:
  - Dong et al., 2009 measured PFCR, which is an assessment of immune function
  - Dong et al. (2011) measured serum levels of IgM, which is an observational immune endpoint and does not address specific antibody function. This effect is less predictive of immunotoxicity than PFCR.

Development of Reference Dose (RfD):
Immune suppression as secondary to other toxicity

Comment: It is unclear whether PFOS is directly immunotoxic or is a result of general toxicity and stress.

Comment: Selection of immune system toxicity is questionable because of presence of systemic toxicity (liver)

- **Response:** Available science supports conclusion that liver toxicity and decreased PFCR caused by PFOS are independent phenomena
- In some studies, decreases in PFCR occurred in the absence of liver effects, and the converse was observed
- Decreased PFCR was not a result of stress in Dong et al. (2009). Increased serum corticosterone (indicator of stress) occurred at an administered dose 10 times greater than the LOAEL for decreased PFCR.

Comment: In the rat study by Lefebvre et al. (2008), hepatic toxicity was more sensitive than immune effects, and hepatic effects from this study should have been considered.

- **Response:** Immunotoxicity of PFOS has not been well characterized in rats.
- The RfD and Health-based MCL based on liver toxicity in Lefebvre et al. (2008) would be about 4-fold lower than those based on Dong et al. (2009)

Development of Reference Dose (RfD):
Relevance of exposure route (dietary versus gavage)

Comment: Daily exposure by oral gavage results in bolus dose that is inconsistent with dietary or drinking water exposures.

- **Response:** Unlike chemicals with a short half-life, a daily bolus dose of PFOS does not cause substantial fluctuations in the serum PFOS levels attained after continued dosing (e.g. 60 days)
- PFOS was delivered in aqueous solution; no delay in absorption as might occur with dietary exposure

Comment: Marty et al. (2007) reported that gavage dosing resulted in an order of magnitude higher blood levels that dietary exposure

- **Response:** Marty et al. (2007) is a studied of chlorpyrifos and its metabolites in rats. Half-life of chlorpyrifos in rats is only several hours, compared to PFOS which has a half-life of 40 to 67 days in rats.
- Difference based on average blood levels is only 3-fold.

Development of Reference Dose (RfD):
Relevance of exposure route (dietary versus gavage) - *continued*

Comment: Gavage studies should not be used for risk assessment of PFOS because a review paper concludes that gavage administration should not be used for endocrine disruptors.

- **Response:** PFOS is not a clear endocrine disruptor and was not mentioned in the review paper. Additionally, this comment refers to compounds including bisphenol A for which toxicokinetics of gavage dosing do not reflect human exposures.
- The review paper discusses that stress from gavage dosing can cause endocrine disruption. The immune system effects of PFOS are not secondary to stress

Comment: Serum PFOS levels that cause hepatic effects are higher with dietary exposure than with gavage exposure.

- **Response:** LOAEL and NOAEL data used to draw this conclusion are from two different species (mouse, rat). Differences in NOAELs/LOAELs are likely due to species differences.
- Ratio of administered dose to serum concentration are similar from dietary study and gavage studies in mice

Development of Reference Dose (RfD):
Relevance of exposure route (dietary versus gavage) - *continued*

Comment: Dietary exposure to environmentally relevant doses did not compromise humoral immune response in Lefebvre et al. (2008)

- **Response:** Differences other than exposure route include: species: rats v. mice; antigen: KLH v. SRBC; assay: foot pad swelling v. PFCR

Comment: Negative findings in dietary study of Qazi et al. (2010) were dismissed from consideration and were not put into context of bolus dosing

- **Response:** Differences other than exposure route include: PFOS salt: tetraethylammonium v. potassium; dose levels: one v. multiple
- Reason for differences in results remain unclear; route of exposure is not likely the cause (dose:serum ratio similar to other studies with positive results)

Development of Reference Dose (RfD):
Point of Departure (POD) from Dong et al. (2009)

Comment: Selection of Dong et al. (2009) is questionable because benchmark dose-response modeling for PFCR response failed to provide an acceptable fit.

- **Response:** According to USEPA Benchmark Dose Modeling Guidance, a NOAEL or LOAEL is used as the POD if a BMDL cannot be developed
- For instance, USEPA (2016) Health Advisories for PFOA and PFOS are based on NOAEL/LOAEL approach

Development of Reference Dose (RfD):
Use of serum PFOS levels as dose metric

Comment: PFOS half-life in humans is several years, while some species excrete PFOS more readily, thus complicating reliance on rodent species in toxicology models

- **Response:** We agree that humans excrete PFOS more slowly than rodents. Therefore, the same external dose results in 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 administered dose, rather than using default uncertainty factor of 3

Development of Reference Dose (RfD):
Development of Target Human Serum Levels

Comment: No context regarding the proposed Target Human Serum Level is provided. The process used is non-standard, as it applies UF directly to animal serum data, and then applies clearance factor.

- **Response:** Approach is used in other PFAS risk assessments, including PFOA risk assessment presented by Tardiff et al. (2009)
- Application of the UF first or last is mathematically identical.

Comment: The derivation and choice of clearance factor in not well-described

- **Response:** Clearance factor, which relates serum PFOS level to human external dose, comes from USEPA (2016) PFOS risk assessment.

Development of Reference Dose (RfD):
Selection of Uncertainty Factors

Comment: Uncertainty factor of 30 is a reasonable choice

- **Response:** Acknowledged

Comment: A UF 3 for of subchronic-to-chronic extrapolation should be applied when a subchronic study is used (Dong et al., 2009 – 60 day)

- **Response:** Studies with varying dosing durations suggest that PFOS causes decreased PFCR within a short timeframe, and this effect does not occur at lower doses with longer dosing duration
- Dose-response is based on serum PFOS levels rather than administered dose.

Development of Reference Dose (RfD):
Calculation of Reference Dose

Comment: The rigorous methodology and criteria used to select a BMDL, or NOAEL if applicable, is scientifically sound and conservative

- **Response:** Acknowledged

Exposures to the fetus, infants, and children

Comment: Setting a standard that minimizes parental fears of contaminating infants and children through breastfeeding and does not dissuade them from breastfeeding is in the public interest and economically sound.

- **Response:** HE Subcommittee agrees with commenter

Comment: PFOS exposures to children from multiple sources, particularly dust exposure, on a body weight basis are likely to be higher than in adults. Literature estimates that contribution of water to total PFOS intake is about the same in adults and two-year olds, about 20%

- **Response:** Agreed with comment on exposures to children from multiple sources. The data provided by commenter provides support for the 20% RSC used in the recommended Health-based MCL

Exposures to the fetus, infants, and children - *continued*

Comment: In addition to greater environmental exposures than adults, children are burdened with PFOS at birth and through breastfeeding

Comment: Early postnatal development must be considered a highly vulnerable period that must be taken into regard when determining exposure limits

- **Response:** These exposures to children are of concern because PFOS causes developmental effects and other effects from short-term exposure. Data demonstrating these effects provide support for a health-protective approach in Health-based MCL development

Exposures to the fetus, infants, and children

Use of children exposure values in Health-based MCL development

Comment: The use of adult default exposure values to determine a MCL does not protect younger children since younger children's dose intakes would exceed the allowable RfD. To assure protection of children, it is important that child specific weight and water intake exposure values be used in the MCL calculation.

- **Response:** Exposure factors for children were not used because of toxicokinetic considerations. 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. 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.
- A RSC of 20%, while not explicitly intended for this purpose, also at least partially account for higher PFOS exposure in young infants. Young infants unlikely to be exposed to PFOS from sources other than prepared formula or breast milk

Comment: Other states' drinking water risk assessments consider higher infant exposures

- **Response:** HE Subcommittee is aware of PFOS risk assessments by Vermont and Minnesota. Vermont's approach is uncertain because of steady state considerations. Use of Minnesota's exposure assumptions for breastfed infants with the DWQI RfD results in a drinking water value close to the DWQI Health-based MCL.

Cancer Risk Assessment

Comment: It is not appropriate to develop a slope factor for liver tumors in rats exposed to PFOS (Butenhoff et al., 2012) because mode of action data indicates a threshold for these tumors.

- **Response:** The mode of action (MOA) for liver tumors caused by PFOS is not known. USEPA Guidelines for Carcinogen risk assessment specify that a linear low-dose extrapolation (slope factor) be used when MOA for tumors is not known.

Comment: The threshold or noncancer approach is supported by high dose and one sex/species finding (Butenhoff et al., 2012) in addition to the lack of significant tumor formation in the recovery group, indicating that once exposure is terminated, progression to tumor formation does not occur

- **Response:** Some of the information in the comment is not accurate. Additionally, observations in the recovery group are not relevant to cancer risk from the Health-based MCL, because the Health-based MCL is based on lifetime exposure.

Mode of Action

Comment: Carcinogenicity of PFOS should be evaluated with USEPA guidance for determining mutagenic MOA and International Programme for Chemical Safety (IPCS) MOA Framework.

- **Response:** EPA mutagenic MOA guidance is not relevant because PFOS is not mutagenic. The HE Subcommittee mode of action analysis is generally consistent with the recommendations in the IPCS framework

Human Epidemiology

Epidemiological data on decreased immune response

Comment: A study in children in the Faroe Islands found maternal cord PFOS levels negatively correlated with anti-diphtheria concentration at 5 years (Grandjean et al. 2012). However, the relevance to other populations is questionable because exposure to other potential immunosuppressants was not accounted for in the study.

- **Response:** Grandjean et al. (2012) state: “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.” and “Most of the PFCs correlated only weakly with PCBs in maternal serum.”

Comment: As described in the Health Canada PFOS assessment, five key epidemiological studies which evaluated PFOS and immune suppression are inconsistent

- **Response:** Studies evaluated different populations and different vaccine types. However, four of five studies found positive association of PFOS with decreases in at least one vaccine antibody. There is no *a priori* reason to expect that the effect of PFOS on all vaccine types would be consistent.

Human Epidemiology

Epidemiological data on decreased immune response

Comment: Health Canada concluded that flaws in epidemiologic database of PFOS and immune suppression impede concluding on a causative mechanism and the nature of the association remains unclear

- **Response:** Human epidemiology data are not used as the primary basis for the Health-based MCL; instead these data provide support for the relevance of animal data to human exposure.
- Three additional studies of infectious disease and PFOS exposure have been evaluated and included in document: Impinen et al. (2018); Dalsager et al. (2016); Goudarzi et al. (2017). They provide further support for human immune effects, and together with other studies provide strong evidence for such effects.
- NTP (2016): “The evidence indicating that PFOS suppresses multiple aspects of the immune system supports the overall conclusion that PFOS alters immune function in humans”

Comment: A cohort of 411 adults did not find an association between serum PFOS levels and antibody response following inactivated trivalent influenza vaccine - Looker et al. (2014)

- **Response:** We agree with this statement. We note that Looker et al. (2014) only evaluated one vaccine type for which no association was found in Granum et al. (2013; the only other study that evaluated it). Looker et al. (2014) is the only study of vaccine response in adults.

Human Epidemiology

Clinical significance of epidemiology data on immune system effects

Comment: Changes in antibody concentrations are subclinical

- **Response:** Fei et al. (2010) found a significant association between hospitalization for infection and PFOS exposure in girls
- Three additional studies (mentioned above) showing association with infections have been added

Human Epidemiology

Immune system effects other than immunosuppression

Comment: Studies have found no association with asthma, allergies, and eczema and PFOS.

- **Response:** NTP (2016) notes that asthma, allergies, and eczema are hypersensitivity responses to the immune system which are qualitatively distinct from the immunosuppressive endpoints
- Lack of consistent data with hypersensitivity does not diminish significance of observed associations with immunosuppression.

Human Epidemiology

Epidemiological data for endocrine and reproductive effects, and for studies in children

Comment: Studies have found associations with PFOA/PFOS and duration of breastfeeding, body weight increase, metabolic rate, type 2 diabetes, renal function, high cholesterol, subfecundity, delayed onset of puberty.

- **Response:** DWQI Health-based MCL Support Document for PFOA includes detailed review of epidemiologic studies
- The Health Effects Subcommittee identified decreased vaccine response, elevated serum uric acid/hyperuricemia, and increased total cholesterol as the human endpoints with sufficient evidence of association with PFOS for purpose of drawing conclusions for Hazard Identification
- Additional confirmatory studies linking additional endpoints to PFOS may support their clear identification as a hazard

Human Epidemiology

Use of human data in quantitative risk assessment

Comment: Human data should be considered/used for establishing a limit for PFOS in drinking water because of extensive epidemiological evidence, fairly crude outcomes measures in toxicology, and would results in a lower drinking water standard

- **Response:** 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 epidemiologic database is insufficient to support the use of this endpoint as the basis for quantitative risk assessment of PFOS. Specifically, strong correlation between PFOA and PFOS limit ability to adjust for both.

Human Epidemiology

Dose-response for decreased vaccine response for PFOS independent of co-occurring PFAS

Comment: Budtz-Jorgensen and Grandjean (2017) demonstrates mutual adjustment of PFOA and PFOS and results only in minor changes

- **Response:** Budtz-Jorgensen and Grandjean (2017) report is not peer-reviewed, and it the only human data set for which BMD analysis has been reported
- It is not clear that the substantial co-exposures of PFOS and PFOA can be effectively separated by statistical means
- Earlier published analysis of same data (Grandjean and Budtz-Jorgensen, 2013) states that the contribution of PFOS and PFOA could not be statistically separated

Protectiveness of Recommended Health-based MCL

Comment: The proposed MCL is not entirely health protective and any additional exposure to drinking water may pose additional risk.

Comment: German Environment Agency in 2016 set a maximum blood plasma concentration of 5 ng/ml which is the estimated median value in the U.S. general population. Any exposure through water would increase exposure over this threshold.

- **Response:** HE Subcommittee agrees that ongoing exposure to Health-based MCL of 13 ng/L is expected to increase PFOS serum levels, and that health effects have been reported at serum PFOS exposures lower than those that will result from MCL of 13 ng/L in drinking water. There is uncertainty regarding protectiveness provided by the Health-based MCL.

Additive toxicity of PFOS and other PFCs

Comment: The additive nature of toxicity from PFOS and other PFC compounds found in NJ water supplies should be considered. An MCL based on the combined concentration of PFC in drinking water should be established.

- **Response:** The potential for additive toxicity is acknowledged by HE Subcommittee. However, the toxicological effects and mode of action for PFOS differ in some respects from other PFCs.
- Treatment removal processes intended to remove a PFOS when the MCL is exceeded may also partially or totally remove other PFCs, other types of PFAS, and/or other unrelated unregulated contaminants.

Consideration of “Rutgers Pilot Study”

Comment: DWQI is urged to evaluate “Rutgers Pilot Study of Perfluorochemical Compounds in Paulsboro Residents” (Sept. 13, 2017) and underlying data

- **Response:** Rutgers study collected data from residents of a community exposed to elevated levels of PFNA in their drinking water - relevance to PFOS risk assessment is unclear
- The cited document is not a full scientific report, but is a brief preliminary report, written in layperson’s language, intended to inform Paulsboro residents

Comment: This report and data will allow direct assessment of assumptions regarding the associations between PFC drinking water concentrations and blood serum levels

- **Response:** Rutgers researcher stated that this study was not intended to, and cannot, provide information on the quantitative relationship between drinking water exposure to PFCs and serum PFC levels. HE Subcommittee agrees with this conclusion
- Reasons include lack of individual-level detailed exposure history to PFCs in drinking water because PFC levels varied by the mixture of wells supplying water to any given location over time