COMMENTS ON NEW JERSEY DRINKING WATER QUALITY INSTITUTE HEALTH-BASED MAXIMUM CONTAMINANT LEVEL FOR PERFLUOROOCTANOIC ACID (PFOA); JUNE 2016

The following are comments on the *Public Review Draft Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA)* developed by the New Jersey Drinking Water Quality Institute (DWQI) Health Effects Subcommittee, dated June 27, 2016. DWQI is recommending a maximum contaminant level (MCL) for PFOA of 0.014 μg/L or parts per billion (ppb), equivalent to 14 parts per trillion (ppt). The MCL, however is based on a number of uncertainties that significantly undermine the scientific merit of DWQI's recommendation, most notably:

1) the decision to select a health effect endpoint in rodents that toxicologists generally concur is not likely to extend to humans;

2) application of an additional uncertainty factor for an effect endpoint that did not actually result in adverse effect in rodents and has uncertain relevance to humans; and

3) an assumption about the relative source contribution of drinking water to total PFOA exposure that is both illogical and contrary to earlier recommendations by the same committee for the health-based MCL for perfluorononanoic acid (PFNA).

This document discusses these specific shortcomings, which we would request that DWQI consider if their final recommendation for a health-based MCL for PFOA is intended to reflect the best available science.

General Comment

Overall, we find the support document to be extremely biased in its characterization of PFOA risks. DWQI did not appropriately handle the uncertainty and inconsistency within the database for health effects associated with PFOA exposure – regarding both the animal toxicity study data and human epidemiology data. DWQI appears to have used data selectively to support its analysis, rather than considering the full weight of evidence.

Studies and findings that support DWQI's conclusions were presented with high confidence and little mention of weaknesses or limitations, while studies and findings that demonstrate inconsistent and/or conflicting interpretations were either not provided or were presented in a manner that over emphasized weaknesses and limitations in those studies. This misrepresentation of PFOA toxicity is found throughout the document and is extremely concerning. The failure to conduct a comprehensive weight-of-evidence review on the full range of data and the selection of a disproportionately low regulatory value for

PFOA, results in unwarranted public concern and economic impacts. The adverse impacts of which to the public have recently been discussed by the Australian Government Department of Health in their selection of interim drinking water guidance values for perfluoroalkyl substances (enHealth 2016).

Specific Comments

The following specific comments highlight the key technical deficiencies in DWQI's approach.

1. **Justification is needed for the selected noncancer endpoints, including transparent and fair representation of the actual adversity of selected endpoints.**

   DWQI presented results from toxicity studies linking PFOA exposure to multiple noncancer endpoints of concern and claimed that they yield relatively consistent points of departure (POD) for calculating a human equivalent dose. However, DWQI did not apply a true weight-of-evidence analysis of the study data, nor a discussion regarding the severity of effects across the range of endpoints.

   A more comprehensive analysis is needed on the following endpoints:

   a. *Immunotoxicity.* Published research findings should be cited that provide the range of "normal" antibody levels in children to establish adversity of the epidemiological studies. Additionally, DWQI should discuss potential confounding factors (i.e., factors other than PFOA exposure) that may contribute to changes in antibody levels. A more transparent discussion is needed regarding the weight-of-evidence of positive and negative findings for this endpoint.

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

   c. *Liver toxicity*. Several regulatory agencies have clearly stated that rodent toxicity studies that demonstrate liver hypertrophy in the absence of cell toxicity or other evidence of potential impairment of liver function are not

suitable for quantifying risks to humans (TOXSAC 2002; Hall et al. 2012). We strongly agree, and recommend that DWQI provide a more transparent presentation of the data showing PFOA-mediated effects on the rodent liver, including a discussion on where actual liver toxicity is or is not observed along the dose-response continuum (see comment 2 below).

2. **At the selected point of departure, liver weight increases in rodents are indicative of exposure rather than effects and there has not been evidence of liver disease in PFOA exposed humans, therefore, liver weight is not an appropriate critical effect from which to derive a health-based MCL.**

   DWQI derived the health-based MCL on increased liver weights in rodents, even though there is strong evidence that at this low dose, the measured change in the liver is an adaptive response associated with normal liver functioning, and not evidence of an adverse effect. Increased liver weight without histopathological changes indicative of cell damage (at the same dose in the same study) should be considered non-adverse. A report by the European Society of Toxicologic Pathology evaluated adverse versus adaptive changes in the liver and concluded that liver weight increases up to 150% of control values may still be considered non-adverse in the context of chemical safety evaluations (Hall et al., 2012). Additionally, the EPA 2002 guidance document from the Health Effects Division Toxicology Science Advisory Council (TOXSAC 2002) notes that a statistically significant increase in liver size alone (i.e., in the absence of histopathological evidence) is not a reliable indicator of hepatic toxicity. In conclusion, the existing data do not clearly support the liver as an appropriate target organ following low level PFOA exposures. Finally, using established toxicology guidance, the data suggest that liver weight changes in the rodents from Loveless et al. (2006) are adaptive, non-adverse effects.

   Additionally, we maintain that the existing data do not clearly link low-level human exposures to PFOA-mediated adverse liver effects in humans. There have not been consistent associations of PFOA with liver biomarkers or liver changes in human studies, including those with serum concentrations equivalent to and much greater than levels used to calculate the proposed MCL. Data from studies of workers with high exposures to PFOA have not demonstrated evidence of increased liver disease and data on liver enzyme parameters have been inconsistent (for example, see Leonard 2003; Sakr et al. 2007; Leonard et al. 2008; Lundin et al. 2009; Steeland and Woskie, 2012). We recommend that DWQI select an alternative effect endpoint for which to base their PFOA MCL.

3. **Stronger justification is needed to support the use of rodent toxicity studies with PFOA to infer comparable dose-response relationship in humans.**

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

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

4. **The limited of evidence on carcinogenic potential of PFOA should be presented more clearly and accurately.**

DWQI significantly overstated the potential link between PFOA exposure and carcinogenicity in humans.

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

b. Additionally, DWQI included the recent IARC cancer evaluation for PFOA, but did not include the recent Health Council of the Netherlands evaluation that concluded that the data are insufficient to make any conclusions regarding the carcinogenicity of PFOA and its salts. Importantly, IARC has recently come under attack from international scientists for their antiquated and inaccurate cancer assessments that do not include a weight-of-evidence approach, do not include all relevant regulatory studies, and that cause unnecessary health scares in the public (Boobis et al. 2016). We recommend a more balanced and fair evaluation of the PFOA carcinogenicity data, taking into consideration the evaluation of the Health Council of the Netherlands (Health Council of the Netherlands 2013), using a true weight-of-evidence analysis, and using only authoritative and recent regulatory references.

c. Despite significant evidence demonstrating no link between human exposures to PFOA and cancer, DWQI summarized the positive studies and ignored conflicting evidence and limitations of studies that do not support DWQI's conclusions. Although the cancer endpoint was not explicitly used to derive the draft MCL, DWQI's cancer discussion for PFOA could contribute to the overall narrative of PFOA as a "cancer causing chemical" in the public perception. We recommend that DWQI provide a more fair and balanced analysis of PFOA potential carcinogenicity, which would lend to the conclusion that there is not a causal association between PFOA exposure and cancer in humans (see also Chang et al. 2014).

d. DWQI's methodology for developing the human equivalent dose from the administered dose in rats from Buttenhoff et al. (2012) is in direct conflict with their study usability criteria for noncancer effects. DWQI stated on pg. 205-206, "Only those studies that provide serum PFOA data were considered for dose-response modeling of non-carcinogenic effects. A risk assessment approach based on measured serum PFOA levels is less uncertain than one based on pharmacokinetic modeling of estimated serum PFOA levels or an approach in which interspecies extrapolations is based on interspecies half-life differences." However, to calculate the cancer-based MCL, the dose in rats corresponding to a 1×10^{-6} cancer risk level was converted to the human equivalent dose using a pharmacokinetic adjustment based on the ratio of half-lives in the two species. In the noncancer portion of their assessment, DWQI acknowledged the extreme uncertainty with this method of dosimetric conversion, and used this criteria to justify excluding numerous studies from evaluation for noncancer effects. However, nowhere in the document did DWQI acknowledge this inconsistency nor discuss the highly uncertain nature of their cancer-based

MCL. We recommend that DWQI apply the same study usability criteria, consistent for both cancer and noncancer evaluations. We also recommend that DWQI thoroughly discuss the uncertainties and limitations in their quantitative cancer analysis.

5. **An extra uncertainty factor of 10 was applied to account for potential developmental toxicity; however, this factor should be removed given the weak evidence for developmental toxicity**.

   Each uncertainty factor applied by DWQI results in a lower MCL. DWQI applied an extra uncertainty factor of 10 to account for potential developmental effects in humans. DWQI based the decision on a PFOA study in rodents in which delayed mammary gland development was observed following perinatal exposure. As DWQI acknowledged, this is a highly uncertain endpoint, with limited support in the rodent toxicology literature and no clear link to human adverse effects.

   DWQI failed to properly discuss the inconsistency present in the various studies addressing this endpoint and failed to disclose the fact that there was no effect on puberty, reproduction, or nursing capabilities of the mice with delayed mammary gland development (Macon et al. 2011), further indicating that the endpoint is highly uncertain and is not biologically significant or adverse.

   Not only does consideration of possible PFOA-mediated developmental effects result in a lower MCL recommendation by the unwarranted extra uncertainty factor, the classification of PFOA as a developmental toxicant contributes to the public's unsupported concern for increased risk for women of childbearing age and infants. DWQI should remove this unnecessary uncertainty factor.

6. **Consistent with EPA guidance (USEPA 2000) and DWQI's analysis for PFNA, DWQI should use PFOA-specific exposure information rather than a default Relative Source Contribution (RSC) of 20 percent**.

   The default RSC of 20% for drinking water is used to calculate health-based MCLs in the absence of additional chemical-specific or site-specific information. DWQI applied this default based on the conclusion that there are insufficient data to develop a chemical-specific RSC for PFOA (pg 215).

   This decision is illogical and inconsistent. Not only is there sufficient information to derive a chemical-specific RSC, DWQI chose to adopt a non-default RSC of 50% for PFNA, despite significantly less PFNA exposure data than is available for PFOA.

   We disagree with DWQI's rationale for the default RSC for PFOA because available data strongly support a higher RSC, similar to the situation for PFNA. Some of the

analysis conducted by DWQI in Appendix 2 can be used to demonstrate a higher RSC for drinking water exposure. Furthermore, the very same publication used by DWQI to support the PFOA clearance factor, Lorber et al. 2011, provides data to support a RSC of between 60 and 70%. It is illogical for DWQI to utilize data from Lorber (2011) for a parameter that impacts the health-based MCL by over 100 fold (i.e., the clearance factor), and not use this same publication and data therein to support a PFOA-specific RSC.

We strongly recommend that DWQI base the RSC on an analysis of PFOA exposure data rather than a default assumption. Furthermore, we recommend that DWQI demonstrate the impact of various RSCs on the final MCL recommendation, using summary statistics from NHANES (e.g., median or 95th percentile) and the Target Human Serum level chosen for the health-based MCL as comparison points.

7. **DWQI appears to conflate two related but very distinct concepts – serum concentrations that exceed background, and serum concentrations that are within a range that may present a health risk. It is inappropriate to present the increase in PFOA serum levels over background serum levels for exposures at select PFOA drinking water concentrations (see Figures E-1, 1 and 8 and associated test) without discussing the uncertainty and variability in the underlying assumptions and without tying serum levels to actual risk.**

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

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

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

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

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

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