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ADDITIONAL PERFLUOROOCTANE SULFONATE (PFOS) COMMENTS

Drinking Water Quality Institute (DWQI) PFOS Subcommittee Reports

Comments on the subcommittee reports are provided below and cover the following key points:

1. 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).
2. DWQI did not consider the effect of exposure duration and route of exposure in their PFOS MCL derivation.
3. 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).
4. DWQI fails to provide any context regarding the proposed Target Human Serum Level.
5. DWQI has not evaluated the feasibility of achieving the MCL, nor has it provided an assessment of the potential utility and efficacy of treatment technologies other than granular activated carbon (GAC).

Health Effects Subcommittee Report

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.

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.

Cancer versus Noncancer Endpoint

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.

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. 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).

Indicator of External Exposure

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.

Dosing Regimes

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.

Table 38 of DWQI's PFOS Health Effects Subcommittee Report

Study	**Endpoint**	**POD (ng/ml)**	**NOAEL (ng/ml)**	**LOAEL (ng/ml)**	***Route/Duration of Exposure***
Butenhoff et al., 2012	Hepatocellular hypertrophy (male rats)	4,560.8 (BMDL)	2,554[a]	11,724[a]	*Dietary, 20 ppm for up to 104 weeks*
Dong et al., 2009	Relative liver weight increase (male mice)	5,585,5 (BMDL)	674	7,132	*Oral gavage, 60 days*
Dong et al., 2012a	Relative liver weight increase (male mice)	4,350 (NOAEL)	4,350	8,210	*Oral gavage, 60 days*
Dong et al., 2009	Decreased plaque forming immune response (male mice)	674 NOAEL)	674	7,132	*Oral gavage, 60 days*
Dong et al., 2011	*Decreases IgM and increases IL-4 cytokine (male mice)*	_____	*2,360*	*10,750*	*Oral gavage, 60 days*
Qazi et al, 2010	*No adverse immune function (male mice)*[b]		*11,600*		*Dietary, 5.55 mg/kg, 28 days*

[a] Based on AUC

[b] Liver toxicity (increased weight liver weight, decreased body weight gain)

Italics – added to DWQI's Draft Document Table 38

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. 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. 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).

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.

Immunotoxicity

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. 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.

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).

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.

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.

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.

As can be seen in the table above, 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 Lebevre 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.

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.

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.

Health-Based MCL Derivation Process

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?).

<u>Treatment Subcommittee Report</u>

Regarding treatment options for PFOS, the Health Effects Subcommittee Report correctly states (first paragraph on page ES-3 and first paragraph on page 9) that, while PFOS and other Perfluorinated Compounds (PFCs) are not effectively removed from drinking water by standard treatment processes, they can be removed from drinking water by GAC or reverse osmosis. However, the report fails to indicate that treatment via anion exchange resin (stand-alone or as a polish to GAC) may also offer significant improvement over stand-alone GAC treatment in terms of both treatment performance and cost effectiveness, particularly for PFOA and PFOS compounds. Since the promise of anion exchange as a treatment option is discussed in the Addendum to Appendix C: Recommendation on Perfluorinated Compound Treatment Options for Drinking Water, as well as the Second Addendum to Appendix C, CCNJ/SRIN recommend that

this treatment option be included in the general discussion in the noted places within the Health Effects Subcommittee Report.

In addition, DWQI does not evaluate the feasibility of water suppliers of all kinds and types across the state implementing carbon or other treatment on their water supplies. This failure means that DWQI has not evaluated the feasibility of implementing the MCL it recommends. This will result in water suppliers increasing costs to consumers in the state of New Jersey to treat the PFOS water.

The 2015 Appendix C document states (page 10) that "USEPA notes that "incineration of the concentrated wastes would be needed for the complete destruction of PFCs" (2014)", which is only a best management practice; there is no discussion of regulatory basis for how this waste may be classified under the Resource Conservation and Recovery Act (RCRA). Any discussion of availability and viability of treatment must consider and discuss regulatory disposal requirements (vs. recommendations) of any waste streams.

References

Hayes, AW. 2007. Principles and Methods of Toxicology (Fifth Edition). August 13.

International Program on Chemical Safety (IPCS). 2008. Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans. October 10.

International Program on Chemical Safety (IPCS). 2008. Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans. October 10.

Marty MS, Domoradzki JY, Hansen SC, Timchalk C, Bartels MJ, Mattsson JL. 2007. The Effect of Route, Vehicle, and Divided Doses on the Pharmacokinetics of Chlorpyrifos and Its Metabolite Trichloropyridinol in Neonatal Sprague-Dawley Rats. *Toxicological Sciences.* 100(2), 360-373.

United States Environmental Protection Agency (USEPA). 2007. Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: Using EPA's 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogen (EPA 120/R-07/002-A). September.

Vandenberg LN, Welshons WV, vom Saal FS, Toutain PL, and Myers JP. 2014. Should oral gavage be abandoned in toxicity testing of endocrine disruptors? *Environ Health*. 13:46. June 25.