BY ELECTRONIC MAIL

February 5, 2018

Ms. Jessie A. Gleason, MSPH
Chair, Health Effects Subcommittee
Drinking Water Quality Institute
NJDEP – Division of Water Supply & Geoscience
Mail Code 401-04Q
401 East State Street
Trenton, NJ 08625

Re: Health-based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS) (CAS # 1763-23-1; Chemical Formula $C_8HF_{17}O_3S$) – Public Review Draft, November 15, 2017

Dear Ms. Gleason:

The Chemical Products and Technology Division of the American Chemistry Council (ACC)[1] appreciates the opportunity to comment on the draft report of the Health Effects Subcommittee (Subcommittee) on perfluorooctane sulfonate (PFOS). ACC represents a number of companies with a strong interest in the science used to develop regulatory standards for PFOS such as the maximum contaminant level (MCL) under consideration within the New Jersey Drinking Water Quality Institute (DWQI or the Institute).

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).[2] 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.[3] Both of these guidelines were developed after a review of the

[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. ACC's Chemical Products and Technology Division is composed of a wide range of more than 60 self-funded product and sector groups that are focused on specific chemistries and related technologies. Members participating in these groups include large and small manufacturers, formulators, downstream users, distributors, suppliers and other trade associations.

[2] USEPA. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). EPA 822-R-16-202 (May 2016).

[3] Health Canada. Perfluorooctane Sulfonate in Drinking Water. Document for public consultation. Prepared by the Federal-Provincial-Territorial Committee on Drinking Water (2016).

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" [4] 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. 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.[5]

Animal Immunological Data are Inconsistent

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. [6] 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."[7] 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."[8] The inconsistency of these study results is detailed below.

The 2008 study by Peden-Adams *et al.* (2008)[9] 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.

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4 Support document, at 319.

5 Ibid, at 325. The Subcommittee's response is to comments provided by USEPA on the state's proposed MCL for PFOA, which the Subcommittee acknowledges apply equally to the approach taken for PFOS.

6 Immune effects in the lone rat study occurred at exposures several orders of magnitude higher than in the mouse studies (3.21 mg/kg/day). Lefebvre DE *et al.* Immunomodulatory effects of dietary potassium perfluorooctane sulfonate (PFOS) exposure in adult Sprague -Dawley rats. *J Toxicol Environ Health A* 71:1516-1525 (2008).

7 USEPA 2016, at 4-7.

8 Health Canada 2016, at 62.

9 Peden-Adams MM *et al.* Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. *Toxicol Sci* 104(1): 144–154 (2008).

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[10], 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 Peden-Adams. No SRBC response was reported in females.

A 2009 study by Zheng *et al.*[11] 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.

In the mouse study by Dong *et al.* (2009),[12] 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. Decreased SRBC response also was reported in C57BL/6 males at 0.083 mg/kg/day – well below the LOAEL reported in the Keil study. In a subsequent study, Dong *et al.* (2011)[13] observed no SRBC response at 0.0167 mg/kg/day.

Human Immunological Data are Inconsistent

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."[14] 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."

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10 Keil DE *et al.* Gestational exposure to perfluorooctane sulfonate suppresses immune function in B6C3F1 mice. *Toxicol Sci* 103(1): 77–85 (2008).

11 Zheng L *et al.* Immunotoxic changes associated with a 7-day oral exposure to perfluorooctanesulfonate (PFOS) in adult male C57BL/6 mice. *Arch Toxicol* 83(7): 679–689 (2009).

12 Dong GH *et al.* Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. *Arch Toxicol* 83(9): 805–815 (2009).

13 Dong *et al.* Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. *Arch Toxicol* 85(10): 1235–1244 (2011).

14 Health Canada 2016, at 61.

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,[15] Grandjean and Budtz-Jørgensen 2013[16]), 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.

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.[17] In contrast, prenatal exposure to PFOS was not associated with hospitalizations for infections in a 2010 Danish cohort study by Fei *et al.*,[18] nor with episodes of common cold, gastroenteritis, eczema or asthma in the Norwegian cohort (Granum *et al.* 2013).

In a Taiwanese cohort study, the median serum PFOS concentration was significantly higher in asthmatic children (Dong *et al.* 2013),[19] and prenatal exposure to PFOS was positively correlated with cord blood Immunoglobulin E (IgE) levels, particularly in male children. However, Wang *et al.* (2011) [20] 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).[21]

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).[22]

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[15] Grandjean *et al.* Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *J Am Med Assoc* 307(4): 391–397. Comment in: *J Am Med Assoc* 307(18): 1910; author reply 1910–1. Erratum in: *J Am Med Assoc* 307(11): 1142 (2012).

[16] Grandjean P and Budtz-Jørgensen E. Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children. Environ. Health, 12: 35 (2013).

[17] Granum B *et al.* Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *J Immunotox* 10(4): 373–379 (2013).

[18] Fei *et al.* Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood. *Environ Res* 110: 773–777 (2010).

[19] Dong *et al.* Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case–control study of Taiwanese children. *Environ Health Perspect* 121(4): 507–513 (2013).

[20] Wang Y *et al.* Modulation of dietary fat on the toxicological effects in thymus and spleen in BALB/c mice exposed to perfluorooctane sulfonate. *Toxicol Lett* 204(2–3): 174–182 (2011).

[21] Okada E *et al.* Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants. *Environ Res* 112: 118–125 (2012).

[22] Looker C *et al.* Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicol Sci* 138: 76–88 (2014).

Vaccine response, as measured by geometric mean antibody titer rise, was not affected by PFOS exposure.

> After reviewing the available human data, Health Canada concluded –
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> 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.[23]

In considering these data USEPA cautioned that "lack of human dosing information . . . precludes the use of these immunotoxicity data in setting the [reference dose]."[24]

<u>The Subcommittee's Conclusions on the Relevance of Animal and Human Evidence are not Supported by the Available Information</u>

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. 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."[25] 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.

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.[26] 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. 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

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[23] Health Canada 2016, at 37.

[24] USEPA 2016, at 4-7.

[25] NTP. Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) or Perfluorooctanoic Sulfonate (PFOS). Office of Health Assessment and Translation. (September 2016), at 1.

[26] Ibid, at 133 (Appendix 3. Risk of Bias Heatmaps).

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.

The Subcommittee points to two 2017 publications as further evidence of the relevance of the immune system effects.[27] 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.

Summary

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. 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. 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.

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.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

[27] Lilienthal et al. (2017) and Dong et al. (2017)