Review of Interim USEPA Health Advisories for PFOA and PFOS and Other Relevant Information

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New Jersey Drinking Water Quality Institute Health Effects Subcommittee:

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EXECUTIVE SUMMARY

New Jersey Department of Environmental Protection (NJDEP) Commissioner Shawn LaTourette requested that the New Jersey Drinking Water Quality Institute (DWQI) review the scientific basis of the United States Environmental Protection Agency (USEPA, 2022a,b) interim drinking water Health Advisories for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). The interim USEPA Health Advisories are health-based drinking water concentrations that do not consider analytical and treatment limitations, and they are below the current New Jersey Practical Quantitation Levels (PQLs) for PFOA and PFOS. Specifically, the DWQI was asked to determine whether current scientific information supports health-based drinking water concentrations below the New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

The Health Effects Subcommittee has reviewed the interim United States Environmental Protection Agency (USEPA, 2022a,b) Health Advisories, the draft USEPA (2021a,b) health effects assessments that provide the basis for the interim Health Advisories, and the USEPA Science Advisory Board (USEPA SAB, 2022)[1] evaluation of the draft USEPA (2021a,b) assessments. Other relevant information was also reviewed including key recent peer-reviewed publications, relevant recent PFOA and PFOS evaluations based on human data by other authoritative organizations, the USEPA (2021c) draft document on approaches for risk assessment of per- and polyfluoroalkyl substances (PFAS) mixtures, and previous Subcommittee conclusions on health effects and risk assessment of PFAS.

While USEPA Health Advisories are based only on non-cancer effects, the USEPA (2021a,b) health effects assessments evaluated both non-carcinogenic and carcinogenic effects. Because New Jersey Health-based Maximum Contaminant Levels (MCLs) consider both non-cancer effects and cancer risk, the Subcommittee considered information on both non-carcinogenic effects and cancer risk in its evaluation.

[1] A member of the Health Effects Subcommittee, Dr. Gloria Post, was a member of the USEPA SAB PFAS Review Panel that drafted the USEPA SAB (2022) report.

The Subcommittee reviewed more recent studies that have become available since the DWQI recommended MCLs for PFOA (DWQI, 2017a) and PFOS (DWQI, 2018) for the following key health effects of PFOA and PFOS in humans: decreased antibody response to vaccination; hepatic effects including increased serum levels of the liver enzyme alanine aminotransferase (ALT), decreased birth weight and related endpoints, increased serum lipids particularly cholesterol, increased risk of cancer, and increased overall mortality. More recent information on exposure to PFOA and PFOS through breast milk and approaches for considering this exposure pathway in drinking water guidelines were also reviewed.

The New Jersey MCLs of 14 ng/L for PFOA and 13 ng/L for PFOS were set at the Health-based MCLs because achievement of the Health-based MCLs was not limited by analytical or treatment removal considerations. The Subcommittee notes that, in contrast to PFOA and PFOS, New Jersey MCLs for numerous other contaminants are set at levels above the Health-based MCL because of analytical and/or treatment removal limitations.

The Subcommittee agrees with the following conclusions from USEPA (2021a,b; 2022a,b) and USEPA SAB (2022) based on its review of these documents and the other relevant information mentioned above:

- Human data are appropriate for use as the basis for non-cancer Reference Doses (RfDs) for PFOA and PFOS and for a cancer slope factor (CSF) for PFOA. The Subcommittee notes that toxicity factors based on human data are generally below those based on animal data.

- The health endpoints with the strongest human evidence for PFOA and PFOS are increased serum cholesterol, decreased antibody response to vaccination, decreased fetal growth (i.e., birth weight), increased serum levels of the liver enzyme ALT, and, for PFOA, increased risk of kidney cancer.

- PFOA is "*Likely to Be Carcinogenic to Humans*" and PFOS has *"Suggestive Evidence of Carcinogenic Potential."*

- A clearance factor (ml/kg/day) should be used to relate external exposures (ng/kg/day) of PFOA and PFOS to internal doses (i.e., blood serum levels; ng/ml), as previously concluded by the Health Effects Subcommittee (DWQI, 2017a, 2018).

- For health endpoints resulting from prenatal and/or early life exposure, a transgenerational toxicokinetic model that considers prenatal exposure and the higher exposures of infants, particularly those who are breastfed, should be used to predict exposures to PFOA and PFOS from drinking water at various life stages.

As discussed in detail in the body of the report, the Subcommittee has concluded that multiple lines of evidence indicate that current scientific information now support Health-based MCLs below the current NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS, as follows:

- As above, the Subcommittee concludes that human data are appropriate for RfD development for PFOA and PFOS. Health-based MCLs for PFOA and PFOS based on RfDs developed from human data by USEPA (2021a,b) and other authoritative agencies based on multiple studies and endpoints are consistently very close to or below the New Jersey PQLs.

- The Subcommittee concludes that increased risk of human kidney cancer is an appropriate basis for a CSF for PFOA. A Health-based MCL for PFOA based on available cancer slope factors for increased risk of human kidney cancer and the one in one million (10^{-6}) cancer risk level used by New Jersey would be far below the New Jersey PQL of 6 ng/L.

- The Subcommittee concludes that previous evaluations by the Health Effects Subcommittee and its members indicate that low dose developmental effects of PFOA in laboratory animals (e.g., delayed mammary gland development in mice) support a Health-based MCL for PFOA below the New Jersey PQL of 6 ng/L.

- The Subcommittee concludes that exposure to PFOA and PFOS in infants is of particular concern because they are a susceptible subpopulation for adverse effects of these PFAS. Consideration of the much higher exposures to PFOA and PFOS in breastfed infants than in older individuals, both within the general population and when drinking water is contaminated, supports Health-based MCLs below the New Jersey PQLs.

- The Subcommittee notes that PFOA, PFOS, and other PFAS typically occur in drinking water as mixtures. It concludes that consideration of toxicological interactions of PFAS that co-occur in drinking water supports more stringent Health-based MCLs than the current values that are based on PFOA and PFOS individually.

The Subcommittee emphasizes that the current Health-based MCLs of 14 ng/L (DWQI, 2017a) for PFOA and 13 ng/L for PFOS (DWQI, 2018) were determined to be public health protective and scientifically supportable based on the information available when they were developed. It further notes that several of the Subcommittee's earlier conclusions (e.g., the relationship between administered dose and serum PFOA/PFOS levels, importance of consideration of exposure to infants through breast milk) were accepted by USEPA in its recent evaluations. Additionally, several other states have used the Subcommittee's conclusions in developing their own drinking water guidelines for PFOA and PFOS.

Finally, as a general recommendation for all MCLs developed by the DWQI, the Subcommittee suggests that PQLs that are above Health-based MCLs should be reevaluated on a regular basis to determine if they can be decreased to closer to or below the Health-based MCL.

INTRODUCTION

The New Jersey Drinking Water Quality Institute (DWQI) previously recommended Maximum Contaminant Levels (MCLs) for three PFAS, and these MCLs were adopted by NJDEP. The New Jersey MCL of 13 ng/L for perfluorononanoic acid (PFNA) was recommended by DWQI in 2015 and was adopted by the New Jersey Department of Environmental Protection (NJDEP) in 2018 (DWQI, 2015; NJDEP, 2018). It was the first MCL to be established for any per- and polyfluoroalkyl substance (PFAS) in the United States. Subsequently, the DWQI recommended MCLs of 14 ng/L for perfluorooctanoic acid (PFOA) in 2017 and 13 ng/L for perfluorooctane sulfonate (PFOS) in 2018, and these MCLs were adopted by NJDEP in 2020 (DWQI, 2017a, 2018; NJDEP, 2020). New Jersey public water systems were required to begin monitoring for PFNA in 2019 and for PFOA and PFOS in 2021. As of November 2022, 12 New Jersey drinking water treatment facilities have installed permanent treatment for removal of PFAS. Permits have been submitted to NJDEP for installation of PFAS treatment at approximately 90 additional facilities. These facilities are in various stages of completing the permitting process and constructing PFAS treatment (NJDEP, 2022a).

In developing MCL recommendations, the DWQI considers health effects (Health-based MCLs), analytical limitations (Practical Quantitation Levels [PQLs]), and treatment removal capabilities. Achievement of the Health-based MCLs of 13 ng/L for PFNA, 14 ng/L for PFOA, and 13 ng/L PFOS was not limited by the PQLs of 5 ng/L for PFNA, 6 ng/L for PFOA, and 4 ng/L for PFOS, and it was determined that available treatment technology can remove these PFAS to levels below the Health-based MCLs. Since achievement of the Health-based MCLs for the three PFAS was not limited by analytical or treatability factors, the MCLs were set at the Health-based MCLs.

On June 15, 2022, the United States Environmental Protection Agency (USEPA) Office of Water issued non-regulatory Health Advisories of 0.004 ng/L (4 parts per quadrillion) for PFOA (USEPA, 2022a) and 0.02 ng/L (20 parts per quadrillion) for PFOS (USEPA, 2022b) and final Health Advisories of 10 ng/L for GenX (hexafluoropropylene oxide dimer acid; USEPA, 2022c) and 2000 ng/L for perfluorobutane sulfonic acid (PFBS; USEPA, 2022d). In contrast to New Jersey and USEPA MCLs, USEPA Health Advisories are health-based drinking water concentrations that do not consider analytical or treatment limitations. The USEPA interim Health Advisories are below the current New Jersey Practical Quantitation Levels (PQLs) for PFOA and PFOS. They are designated as "interim" because they are based on draft USEPA PFOA and PFOS (2021a,b) RfDs that were under review by the USEPA Science Advisory Board (SAB)[2]. The health effects assessments for GenX and PFBS (USEPA, 2021d,e) are final.

USEPA has announced that the final PFOA and PFOS Health Advisories will differ from the interim Health Advisories, but that they are expected to remain below the USEPA analytical

[2] The USEPA SAB is an external advisory body that provides scientific advice and peer review to USEPA. A member of the Health Effects Subcommittee, Dr. Gloria Post, was a member of the USEPA SAB PFAS Review Panel that drafted the USEPA SAB (2022) report.

Minimum Reporting Levels (MRLs) of 4 ng/L (USEPA, 2022f). USEPA has also stated that the interim PFOA and PFOS Health Advisories supersede the earlier USEPA (2016a,b) PFOA and PFOS Health Advisories of 70 ng/L for PFOA, PFOS, and the total of both compounds (USEPA, 2022c); there were no previous USEPA Health Advisories for GenX or PFBS.

The final USEPA PFOA and PFOS health effects assessments will provide the basis for the Maximum Contaminant Level Goals (MCLGs) for the National Primary Drinking Water Regulations (Maximum Contaminant Levels [MCLs] or Treatment Technique) for PFOA and PFOS that USEPA plans to propose by the end of 2022 (USEPA, 2022f). Because state standards may not be higher than federal standards, the final National Primary Drinking Water Regulations, when adopted by USEPA, will supersede the New Jersey MCLs if they are lower than the NJ MCLs.

In a letter to the DWQI Chair, Dr. Keith Cooper, dated June 21, 2022 (NJDEP, 2022b), NJDEP Commissioner Shawn LaTourette requested that the DWQI review the scientific basis of the Health Advisories for four PFAS that had been issued by USEPA (USEPA, 2022e). It was requested that the DWQI's review of the interim Health Advisories for PFOA and PFOS be prioritized, followed by review of the Health Advisories for PFBS and GenX. The Commissioner's letter asked that the DWQI determine whether current scientific information supports health-based drinking water levels below the current New Jersey Practical Quantitation Levels (PQLs) of 6 ng/L for PFOA and 4 ng/L for PFOS. The letter further requested that, if the DWQI concludes that health-based drinking water levels below current NJ PQLs are supportable, the DWQI should reevaluate the PQLs for PFOA and PFOS. Finally, if updated PQLs are developed, the DWQI should determine whether they are achievable with current treatment removal technology.

The Subcommittee was not asked to identify numerical values for updated Health-based MCLs for PFOA and PFOS. For this reason, the Subcommittee did not undertake development of updated Health-based MCLs or identification of specific study(ies) or health endpoint(s) to be used as the basis for updated Health-based MCLs for PFOA and PFOS. Instead, the Subcommittee focused on the more general question of whether health-based drinking water levels below the current NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS are scientifically supportable.

To this end, the Subcommittee reviewed the interim USEPA health advisories for PFOA and PFOS (USEPA 2022a,b), the draft USEPA health effects assessments (USEPA 2021a, b) which provide the support for the interim USEPA Health Advisories, the USEPA Science Advisory Board (USEPA SAB, 2022) review of the draft USEPA health assessments, and other key recent peer-reviewed publications not considered by USEPA.

While USEPA Health Advisories are based only on non-cancer effects, the USEPA (2021a,b) health effects assessments evaluate both non-carcinogenic and carcinogenic effects. Because New Jersey Health-based MCLs consider both non-carcinogenic effects and cancer risk, the Subcommittee considered information on both types of effects in its evaluation. Specifically, the

Subcommittee review of key recent peer-reviewed publication focused on the following key health effects of PFOA and PFOS in humans: decreased antibody response to vaccination; hepatic effects including increased serum ALT, decreased birth weight and related endpoints, increased serum lipids particularly cholesterol, increased risk of cancer, and increased overall mortality.

Further, the Subcommittee reviewed relevant recent PFOA and PFOS evaluations based on human data by other authoritative organizations, the draft USEPA (2021c) document on approaches for risk assessment of PFAS mixtures, and previous Subcommittee conclusions on PFAS health effects and risk assessment. More recent information on exposure to PFOA and PFOS through breast milk and approaches for considering this exposure pathway in drinking water guidelines were also reviewed.

USEPA (2022a,b) INTERIM HEALTH ADVISORIES, USEPA (2021a,b) HEALTH EFFECTS ASSESSMENTS, AND USEPA SAB (2022) REVIEW

USEPA (2022a,b) Interim Health Advisories

The interim Health Advisories of 0.004 ng/L for PFOA and 0.02 ng/L for PFOS are dramatically lower (>4 and >3 orders of magnitude for PFOA and PFOS, respectively) than the earlier Health Advisories of 70 ng/L for PFOA or PFOS individually and the total concentration of both USEPA (2016a,b). In a press release issued by the USEPA in June 2022, the USEPA stated that adverse health effects may occur from PFOA and PFOS concentrations in drinking water that are "near zero" (USEPA, 2022g). The interim Health Advisories are also far below the USEPA drinking water MRLs of 4 ng/L for both PFOA and PFOS, meaning that the Health Advisory is exceeded if there is any detection of PFOA or PFOS in drinking water analyzed with the USEPA methods (USEPA, 2022a,b).

The interim Health Advisories are based on draft Reference Doses (RfDs) for decreased vaccine response in children, which was identified as the most sensitive non-cancer endpoint in the draft USEPA (2021a,b) health effects assessments of PFOA and PFOS (see below); carcinogenic effects are not considered in USEPA Health Advisories. The interim Health Advisories use a Relative Source Contribution (RSC) factor of 20% (the default value and most stringent possible option), as recommended in the USEPA (2021a,b) assessments. The USEPA (2021a,b) assessments did not recommend drinking water exposure assumptions (drinking water ingestion rate based on daily volume of drinking water ingested and body weight), and the interim Health Advisories use the 90th percentile drinking water consumption rate (direct and indirect consumption of community water, consumers only) for children aged 0 to < 5 years, which is 0.0701 L/kg/day (USEPA, 2019).

Because the Interim Health Advisories are based on adverse effects resulting from short-term exposure in children, they are applicable to short-term (weeks to months) exposures to PFOA and PFOS in drinking water (USEPA, 2022a,b). The Health Advisories are also stated to be protective for lifetime (chronic) exposure because decreased vaccine response from short-term

exposure in children was identified as a more sensitive endpoint than any other non-cancer effect, including chronic effects (USEPA, 2022a,b).

The USEPA (2022a,b) Health Advisories are designated as "interim" because they are based on draft USEPA (2021a,b) PFOA and PFOS RfDs that were under review by the USEPA SAB (see below). Importantly, USEPA (2022f)[3] has stated that the PFOA and PFOS toxicity factors (RfDs, CSF) and Health Advisories will change in response to the USEPA SAB (2022) recommendations but that the revised Health Advisories and the MCLGs that are under development are likely to remain below the USEPA MRLs for PFOA and PFOS of 4 ng/L.

Additionally, although Health Advisories do not consider cancer risk, health-based drinking water concentrations for PFOA based on cancer risk at the 1 in 1 million (1×10^{-6}) risk level and the USEPA (2021a) CSFs would be below the current New Jersey PQL of 6 ng/L. This is discussed further below in the section on the USEPA (2021a,b) carcinogenicity evaluations below.

Draft USEPA PFOA and PFOS health effects assessments (USEPA, 2021a,b) and USEPA SAB (2022) review

The draft USEPA (2021a,b) health effects assessments developed updated RfDs for PFOA and PFOS. They also evaluate the weight of evidence for carcinogenicity for PFOA and PFOS, and developed a cancer slope factor [CSF] for PFOA. These RfDs and CSF are based on human data from epidemiological studies in the general population, and they are much more stringent than earlier USEPA (2016a,b) toxicity factors which are based on animal studies. The draft RfDs were used as the basis of the USEPA (2022a,b) interim Health Advisories; as noted above, Health Advisories do not consider carcinogenic effects.

The Subcommittee's review of the recent USEPA (2021a,b) health effects assessments included consideration of the USEPA SAB (2022) review of those assessments. The USEPA SAB is an external advisory body to USEPA that provides "independent scientific and technical peer review and advice to the [US]EPA administrator." (USEPA, 2022h). One of the SAB's responsibilities is to "review the quality and relevance of the scientific and technical information being used by the EPA or proposed as the basis for Agency regulations (USEPA, 2022i)." The EPA Office of Water requested that the SAB review the draft USEPA (2021a,b) health assessments for PFOA and PFOS. The USEPA SAB (2022) agreed with the major conclusions of the USEPA (2021a,b) PFOA and PFOS health effects assessments including the following key considerations: use of human data as the basis for toxicity factors (RfDs, CSF), appropriateness of decreased antibody response to vaccines as a critical effect for Reference Doses, and classification of PFOA as *Likely to be Carcinogenic to Humans.* However, the USEPA SAB (2022) made extensive recommendations for strengthening the scientific basis for the USEPA

[3] This was stated by USEPA in a presentation (USEPA, 2022f) to the USEPA Science Advisory Board.

(2021a,b) conclusions including, among many others, that multiple endpoints be considered for RfD development and data from multiple studies be considered for CSF development.

After revision in response to USEPA SAB (2022) recommendations, the final USEPA health effects assessments will provide the basis of the MCLGs for the National Primary Drinking Water Regulation (MCL or Treatment Technique) for PFOA and PFOS that USEPA plans to propose in Fall 2022 and finalize in Fall 2023 (USEPA, 2022f). As discussed above, while USEPA Health Advisories are based only on non-cancer effects, USEPA MCLGs consider both non-carcinogenic and carcinogenic effects. Therefore, the USEPA (2021a,b) health effects assessments evaluated both non-cancer effects and carcinogenicity of PFOA and PFOS.

As discussed in detail in the sections below, the Subcommittee has concluded that multiple lines of evidence presented in USEPA (2021a,b) indicate that current scientific information now support Health-based MCLs below the current NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS. Specifically, the Subcommittee agrees with USEPA (2021a,b) that human data are an appropriate basis for toxicity factors for PFOA and PFOS. Furthermore, health-based drinking water concentrations using the range of potential RfDs for PFOA and PFOS and the CSF for PFOA developed from human data by USEPA (2021a,b) are below the current New Jersey PQLs.

Use of human epidemiological data as the basis for toxicity factors

An important conclusion of the USEPA (2021a,b) health effects assessments is that human data is appropriate for use as the basis for RfDs for PFOA and PFOS and the CSF for PFOA, and the USEPA SAB (2022) agreed with this conclusion. The use of human data represents a major change from the previous USEPA (2016a,b) assessments in which toxicity factors were based on laboratory animal data. This decision is important because PFOA and PFOS toxicity factors based on human data are generally far below those based on animal data.

The earlier USEPA (2016a,b) PFOA and PFOS assessments concluded that there was epidemiological evidence for associations between PFOA and/or PFOS and several health endpoints (serum lipids, antibody response to vaccination, fetal growth and development, hepatic effects [PFOA], and thyroid effects [PFOS]), with the strongest evidence for serum lipids, reproductive parameters, and (for PFOA) immunotoxicity. However, USEPA (2016a,b) stated that these human studies could not be used for the dose-response modeling needed for toxicity factor development because no information on external exposure was available and the serum PFOA/PFOS levels in the studies were not an appropriate exposure metric. Relevant to this issue, USEPA's comments to the DWQI (USEPA, 2016c) disagreed with the DWQI Health Effects Subcommittee (2017a) conclusion that serum PFOA levels can be related to external PFOA exposure at levels found in the environment (e.g., in drinking water) by the clearance factor (L/kg/day) presented in the USEPA (2016a) PFOA assessment. USEPA stated that the clearance factor could be used only to convert the much higher serum PFOA levels from laboratory animal studies to human equivalent doses and that it could not be used to evaluate environmental exposures. However, as noted by DWQI (2017b), USEPA scientists (Lorber and Egeghy, 2011)

developed the PFOA clearance factor and used it to evaluate the relationship between PFOA exposures and serum levels in the general population including increases in serum PFOA from drinking water exposures in the same manner as DWQI (2017a).

USEPA (2021a,b) disagreed with the earlier USEPA (2016a,b) conclusion that the relationship between external exposures and human serum PFOA and PFOS levels cannot be determined. Consistent with the conclusions of DWQI (2017a, 2018) discussed below, USEPA (2021a,b) identified the POD-Human Equivalent Dose (POD_{HED}) in terms of serum PFOA/PFOS levels (ng/ml) for several cancer and non-cancer endpoints from human and animal studies and used clearance factors to determine the administered doses (Human Equivalent Doses) that would result in these serum levels.

Points of Departure and Reference Doses (RfDs) for non-cancer effects

USEPA (2021a,b) and the USEPA SAB (2022) concluded that the non-cancer endpoints with the strongest epidemiological evidence for associations with PFOA and/or PFOS are increased serum cholesterol, increased serum levels of the liver enzyme ALT, decreased fetal growth (i.e., birth weight), and decreased antibody response to vaccines. These USEPA (2021a,b) and USEPA SAB (2022) conclusions are generally consistent with the conclusions of the DWQI (2017a, 2018).

The USEPA SAB (2022) further noted that although most studies did not evaluate the number of subjects with a clinically abnormal value for these endpoints, one or more study of each of the four endpoints reported an association of PFOA and/or PFOS with increased risk of a clinically abnormal value (e.g., clinically defined high cholesterol [hypercholesteremia]; clinically defined elevated ALT; clinically defined low birth weight [LBW] or small for gestational age [SGA]; levels of antibodies to vaccines below a clinically protective level). Associations of PFOA and PFOS with all four of these endpoints are reported in studies from the general population, not only in occupational studies or communities with contaminated drinking where exposures are higher.

USEPA (2021a,b) identified PODs in terms of serum PFOA/PFOS level (ng/ml) for decreased antibody response to vaccines, increased serum cholesterol, and decreased birth weight from several epidemiological studies from the general population. The USEPA SAB (2022) supported this approach and recommended that PODs for increased serum levels of the liver enzyme ALT in human studies also be developed, since increased ALT is an adverse effect that is a marker for liver disease.

For human effects resulting from chronic exposure, USEPA (2021a,b) assumed that serum PFOA and PFOS levels were at steady state and used a clearance factor to derive the POD_{HED} in terms of external dose (ng/kg/day) from the serum level PODs. For effects resulting from exposures during development, including exposures to the fetus, infant, or child, a toxicokinetic model that accounts for exposure to the pregnant woman, the developing fetus, and the higher exposure to the breastfed infant was used. Recognition by USEPA (2021a,b) of the

importance of exposure through breast milk is particularly important since, as discussed in detail below, serum PFAS levels in the breastfed infant are much higher than maternal serum levels, particularly for PFOA.

The range of USEPA (2021a,b) $PODs_{HED}$ from human studies for various endpoints is 0.00149 - 1 ng/kg/day for PFOA and 0.0791 - 8.95 ng/kg/day for PFOS. Applying the default uncertainty factor of 10 for intra-individual variation to these $PODs_{HED}$ results in potential RfDs of 0.000149 – 0.1 ng/kg/day for PFOA and 0.00791 ng/kg/day – 0.895 ng/kg/day for PFOS. Using default adult drinking water exposure assumptions (2.4 L/day water ingestion; 80 kg body weight, which are less conservative than assumptions for infants, children, or lactating women, and the default RSC of 0.2, the health-based drinking water values based on even the highest potential RfDs (0.1 ng/kg/day for PFOA and 0.895 ng/kg/day for PFOS) are 0.67 ng/L for PFOA and 6 ng/L for PFOS, close to or below the NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS. Relevant to these points, USEPA (2022f) has stated that the final USEPA health-based drinking water levels will differ from the interim Health Advisories, but that they are expected to remain below the USEPA Reporting Levels of 4 ng/L for PFOA and PFOS.

The most sensitive (lowest) PODs and $PODs_{HED}$ developed by USEPA (2021a,b) are for associations of serum PFOA and PFOS levels in 5 year old children from the general population with decreased antibody response to tetanus (PFOA) or diphtheria (PFOS) vaccination at age 7 years (Grandjean et al., 2012). Because these were the most sensitive non-cancer endpoints, USEPA (2021a,b) selected these effects as the critical endpoints for their draft RfDs, and the USEPA SAB (2022) agreed that this endpoint is appropriate for use as basis for RfDs.

The PODs for the critical endpoints are $BMDLs_5$ (i.e., BMDLs based on a Benchmark Response of 5%) in terms of PFOA and PFOS serum levels published by Budtz-Jorgensen and Grandjean (2018) of 0.17 ng/mL for response to tetanus vaccine for PFOA and 0.54 ng/L for response to diphtheria vaccine for PFOS. These $BMDLs_5$ were converted to $PODs_{HED}$ of 0.015 ng/kg/day for PFOA and 0.079 ng/kg/day for PFOS using a toxicokinetic model, and these are the lowest (most stringent) of the $PODs_{HED}$ presented in USEPA (2021a,b). To develop the draft RfDs, USEPA (2021a,b) applied an uncertainty factor of 10 for intra-human variability to the $PODs_{HED}$. The resulting draft RfDs are 0.0015 ng/kg/day for PFOA and 0.0079 ng/kg/day for PFOS. These RfDs are much lower than the earlier USEPA and New Jersey RfDs based on toxicological effects in laboratory animals which were 20 ng/kg/day for both PFOA and PFOS (USEPA, 2016a,b) and 2 ng/kg/day for PFOA and 1.8 ng/kg/day for PFOS (DWQI, 2017a, 2018). Health-based MCLs based on these RfDs would be far below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

Because the draft RfDs are based on adverse effects resulting from short-term exposure in children, they are applicable to short-term exposures to PFOA and PFOS in drinking water (SAB, 2022). They are also protective for lifetime (chronic) exposure because the critical endpoint, decreased vaccine response from short-term exposure in children, was identified as a more sensitive endpoint than any other non-cancer effects, including chronic effects (USEPA, 2021a,b).

As mentioned above, the USEPA SAB (2022) agreed with the use of human data as the basis for toxicity factors for PFOA and PFOS and supported the use decreased antibody response to vaccines as the critical effect for Reference Doses. However, USEPA SAB (2022) noted that the basis for the BMD modeling performed by Budtz-Jorgensen and Grandjean (2018) was not provided in that publication or the draft USEPA (2021a,b) documents. The USEPA SAB (2022) recommended that USEPA provide the detailed basis of the BMD modeling, and USEPA has stated that they have received the modeling details from the authors and that they are currently reviewing it.

Additionally, the USEPA SAB (2022) recommended that multiple human endpoints, rather than just a single one, be considered in RfD development and noted that the level of evidence is similar for associations of PFOA and PFOS with decreased vaccine response, decreased birth weight, increased serum cholesterol, and increased serum ALT. One reason for this recommendation is that potential confounding (for example, by inter-individual physiological differences that affect both serum PFAS levels and the health effect being evaluated) is unlikely to affect all of the health effects endpoints of interest. Specifically, the USEPA SAB (2022) stated: "Considering multiple studies of a variety of endpoints in different populations would provide convergent evidence that is more reliable than any one study or health endpoint in isolation."

As above, USEPA (2022f) has stated that they are revising their PFOA and PFOS assessments to address the USEPA SAB (2022) recommendations. They have stated that the final RfDs for PFOA and PFOS will differ from the draft values, but that the MCLGs based on the final RfDs are anticipated to remain below the Reporting Levels of 4 ng/L.

Carcinogenicity evaluations

USEPA (2021a,b) concluded that currently available data indicates that PFOA is *Likely to be Carcinogenic to Humans* under the USEPA (2005) Guidelines for Carcinogen Risk Assessment, and the USEPA SAB (2022) agreed with this conclusion. This is a change from the USEPA (2016a) conclusion that PFOA has *Suggestive Evidence of Carcinogenic Potential*, and it is supported by additional recent evidence for carcinogenicity of PFOA in both humans (Shearer et al., 2021) and animals (NTP, 2020).

USEPA (2021a) developed draft central tendency and upper confidence limit CSFs from dose-response data for the association of increased risk of renal cell carcinoma with serum PFOA levels in the U.S. general population (Shearer et al., 2021), and the USEPA SAB (2022) agreed that human data should be considered at the basis for the PFOA CSF. The USEPA (2021a) CSFs in terms of serum PFOA level $(ng/ml)^{-1}$ are 0.00178 $(ng/ml)^{-1}$ for the central tendency estimate and 0.00352 $(ng/ml)^{-1}$ for the 95th percentile upper confidence limit. These CSFs in terms of external dose $(mg/kg/day)^{-1}$ were developed by applying a clearance factor of 0.12 ml/kg/day to the serum level CSFs. They are 0.01483 $(ng/kg/day)^{-1}$ or 14,380 $(mg/kg/day)^{-1}$ (central tendency estimate) and 0.0293 $(ng/kg/day)^{-1}$ or 29,300 $(mg/kg/day)^{-1}$ (95th percentile upper confidence limit). The draft USEPA (2021a) CSFs based on human data from Shearer et al. (2021) are more

than six orders of magnitude more stringent than the earlier USEPA (2016a) CSF of 0.07 $(mg/kg/day)^{-1}$ based on testicular tumors in rats (Butenhoff et al., 2012).

USEPA (2021a) also updated its PFOA CSF based on animal tumor data. As noted above, the USEPA (2016a) CSF for PFOA was 0.07 $(mg/kg/day)^{-1}$, based on testicular tumors in rats (Butenhoff et al., 2012), and the DWQI (2017a) CSF from the same data is 2.52 $(mg/kg/day)^{-1}$. The USEPA (2016a) CSF is 36-fold less stringent than the DWQI (2017a) CSF because USEPA did not consider the much longer half-life of PFOA in rats than humans and used the default (body weight$^{3/4}$) approach for interspecies toxicokinetic extrapolation while DWQI accounted for the much longer human half-life; this approach did not consider the much higher internal dose in humans as compared to rats from the same administered dose. USEPA (2021a) updated the CSF for testicular tumors in rats from Butenhoff et al. (2012) to 12.2 $(mg/kg/day)^{-1}$ and now considers interspecies half-life differences in development of the updated CSF. USEPA (2021a) also developed CSFs of 9.4 $(mg/kg/day)^{-1}$ for hepatic tumors and 53 $(mg/kg/day)^{-1}$ for pancreatic acinar tumors in male rats in a more recent NTP (2020) study.

The health-based drinking water concentrations for PFOA based on the draft USEPA (2021a) CSFs for either human or animal tumor data and the 1 in 1 million (1×10^{-6}) cancer risk level and exposure assumptions (2.4 L/day water ingestion: 80 kg body weight; DWQI, 2021) used by New Jersey would be below the current New Jersey PQL of 6 ng/L. Specifically, they would be 0.002 ng/L based on the central tendency estimate human CSF of 14,380 $(mg/kg/day)^{-1}$ and 0.62-2.1 ng/L based on the rat CSFs of 9.4-53 $(mg/kg/day)^{-1}$.

It should be noted that the USEPA SAB (2022) made recommendations for USEPA regarding development of the CSF for PFOA including consideration of multiple studies. USEPA (2022f) has stated that the CSF for PFOA is under review in response to the USEPA SAB (2022) comments and that the numerical values are likely to change when it is finalized. That being said, it is anticipated that the Health-based MCL based on the revised CSF and the 1 in 1 million (1×10^{-6}) cancer risk level will be substantially below the New Jersey PQL of 6 ng/L.

For PFOS, USEPA (2021b) agreed with the earlier USEPA (2016b) conclusions that there is *Suggestive Evidence of Carcinogenic Potential* and that available data do not support development of a CSF, and the USEPA SAB (2022) agreed with this conclusion.

Consideration of co-exposure to multiple PFAS

An important issue regarding use of human data as the basis for PFOA and PFOS toxicity factors is quantitatively accounting for co-exposure to multiple PFAS. This issue was noted by USEPA (2016a,b; 2021a,b), DWQI (2017a, 2018), and the USEPA SAB (2022). Serum levels of multiple PFAS are often correlated, and special modeling approaches are needed to determine the quantitative contributions of individual PFAS to observed associations of multiple co-occurring PFAS with health endpoints.

As stated by USEPA SAB (2022): "While not necessarily acting as a conventional confounder (i.e., an independent cause of the outcome), this [co-exposure to other PFAS that cause the same

health effect] would distort the quantitative estimates for dose-response modeling. An effect attributed to a given change in one form of PFAS might in fact be in part a function of other forms of PFAS that are associated with it. If this were the case, then the actual potencies of PFOA or PFOS would be lower than implied by the studies."

The PODs for decreased vaccine response in children (Grandjean et al., 2012) used for the draft USEPA (2021a,b) Reference Doses are a BMDL (lower confidence limit on the BMD) for PFOA that is adjusted for PFOS and a BMDL for PFOS that is adjusted for PFOA (Budtz-Jorgensen and Grandjean, 2018). The values of these adjusted PFOA and PFOS BMDLs are similar to the unadjusted BMDLs for PFOA and PFOS.

As stated above, co-exposure to other PFAS might increase the apparent individual potencies of PFOA and PFOS. Although this issue is relevant to determination of specific numerical values for Reference Doses based on human data, the possibility of lower actual potencies of PFOA and/or PFOS is not anticipated to negate the Health Effects Subcommittee's conclusion that health-based drinking water levels below 6 ng/L for PFOA and 4 ng/L for PFOS are scientifically supportable.

Also relevant to PFAS that co-occur in drinking water, it is noted that the New Jersey Health-based MCLs and MCLs for PFOA and PFOS (DWQI, 2017a, 2018) do not account for potential toxicological interactions (e.g., additive toxicity) of multiple PFAS that cause the same health effects, resulting in less stringent values than if co-exposure to other PFAS had been considered. USEPA (2021c) proposed an approach for the evaluation of non-cancer risks of mixtures of PFAS in drinking water and other environmental media, and this approach was generally supported by USEPA SAB (2022). This topic is further discussed in the section on assessment of risks of mixtures of PFAS and related appendix, below.

PREVIOUS RELEVANT HEALTH EFFECTS SUBCOMMITTEE CONCLUSIONS

A detailed review of previous Health Effects Subcommittee conclusions relevant to the current evaluation presented in this memorandum is found in Appendix 1 (page 30). This section provides a summary of this information.

The Health Effects Subcommittee first evaluated PFOA in 2009-10. The conclusions of this initial evaluation, which are also relevant to PFOS, provided an initial foundation for the Subcommittee's current consideration of whether stringent health-based drinking water levels for PFOA and PFOS are scientifically supportable. Specifically, the Subcommittee recognized that PFOA is bioaccumulative in humans and that this bioaccumulation is a major contributor to PFOA's toxicity at low doses. This is because a given administered dose or drinking water concentration of a bioaccumulative contaminant such as PFOA results in a much higher human body burden (i.e., internal dose) than the same administered dose/drinking water concentration of a non-bioaccumulative contaminant. The Subcommittee also concluded that the limited data available at the time demonstrated associations of human health effects with PFOA exposures within the general population range and that PFOA caused low-dose toxicity in laboratory

animals. The Subcommittee further emphasized that exposures to PFOA and other PFAS in infants, particularly those who are breastfed, are much higher than in older individuals and that these higher exposures are of concern because infants are a susceptible subpopulation for effects of PFAS. The Subcommittee formed these conclusions well before they were widely acknowledged or accepted by other regulatory authorities or the general scientific community. These conclusions were included in the Subcommittee's 2010 internal draft Health-based MCL Support Document (DWQI, 2010a) and a peer-reviewed publication (Post et al., 2009) whose authors included two current Subcommittee members (G. Post and K. Cooper). Subsequent Health Effects Subcommittee evaluations (DWQI, 2017a, 2018) and peer-reviewed publications by current Subcommittee members (Post, Cohn, Cooper, 2012; Post, Gleason, Cooper, 2017; Post, 2022) discuss more recent data that further supports these conclusions.

The Subcommittee's final Health-based MCL Support Documents for PFOA (DWQI, 2017a) and PFOS (DWQI, 2018) concluded that these PFAS are associated with several human health effects within the general population exposure range even without additional exposure from drinking water, with evidence supporting criteria for causality for some of these endpoints. The Subcommittee also concluded that the human epidemiology data available at the time when the Support Documents were written had limitations that precluded their use as the quantitative basis for the Health-based MCLs. While recognizing the limitations of the data for use in quantitative risk assessment, the Subcommittee further concluded that the human data "suggest that continued human exposure to even relatively low concentrations of PFOA in drinking water results in elevated body burdens that increase the risk of health effects, indicating a need for caution about exposures from drinking water."

Additionally, the final Health-based MCL Support Document for PFOA (DWQI, 2017a) concluded that toxicological data from animal studies also support a stringent health-based drinking water concentration for PFOA. The Target Human Serum Level of 0.8 ng/ml and associated Reference Dose of 0.11 ng/kg/day for delayed mammary gland development in mice (Macon et al., 2011) were below the average PFOA exposure levels in the general population, with several other toxicological effects in animal studies reported at similarly low doses. Although a Health-based MCL based on delayed mammary gland development was not recommended for reasons discussed in Appendix 1 of this memorandum, the Health-based MCL based on this Reference Dose using the default adult drinking water exposure assumptions used at that time (2 L/day water consumption, 70 kg body weight, 20% Relative Source Contribution) would be 0.88 ng/L, and it would be lower if a higher drinking water ingestion rate (L/kg/day) for a sensitive life stage were used.

Based on the information summarized above, the Health Effects Subcommittee (DWQI, 2017a, 2018) concluded that "additional exposure [to PFOA or PFOS] from drinking water may potentially pose some risk of health effects. For this reason, it could not definitively be concluded that lifetime exposure to … [the Health-based MCLs of 14 ng/L for PFOA and 13 ng/L for PFOS] is protective of sensitive subpopulations with a margin of exposure." The more recent information reviewed in the evaluation presented herein further supports this conclusion

and indicates that Health-based MCLs below the current NJ MCLs of 6 ng/L for PFOA and 4 ng/L for PFOS are scientifically supportable.

USE OF HUMAN DATA IN PFOA AND PFOS EVALUATIONS BY OTHER AUTHORITATIVE AGENCIES

Until recently, all toxicity factors and drinking water guidelines developed by federal, state, and international agencies for PFOA and PFOS were based on animal toxicology data. In addition to USEPA (2021a,b; 2022a,b), recent evaluations from several other authoritative groups including the European Food Safety Authority (EFSA, 2020), California EPA (CalEPA, 2021), and National Academy of Sciences and Medicine (NASEM, 2022) have also concluded that human epidemiological data for associations of health effects with PFOA and PFOS are appropriate as the basis for toxicity factors, drinking water guidelines, and/or other public health advice related to exposure to these and other PFAS.[4] Because human health effects are associated with very low exposures to PFOA and PFOS, toxicity factors and drinking water guidelines for PFOA and PFOS based on human data are generally more stringent than those based on animal data.

Table 1 summarizes key information from the EFSA (2020), CalEPA (2021), and NASEM (2022) evaluations, and detailed information is provided in Appendix 2 (page 36). As shown in Table 1, the conclusions and the numerical values developed by these authoritative groups provide additional support for health-based drinking water levels below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

[4] It is also noted that the Minnesota Department of Health (MDH, 2022) recently announced that it is reevaluating PFOA and PFOS and stated in a September 29, 2022 email that its review will focus on data from human epidemiological studies.

Table 1. PFAS health effects evaluations based on human epidemiology data by organizations other than USEPA

Organization	PFAS included	Health-based Value	Basis	Drinking Water Exposure Assumptions**	Health-based Drinking Water Concentration (ng/L)**
European Food Safety Authority (2020)	Total of PFOA, PFOS, PFNA, PFHxS	Tolerable Daily Intake* 0.63 ng/kg/day	Maternal exposure resulting in decreased antibody response to vaccines in breastfed children at age one year (Abraham et al., 2020)	0.0354 L/kg/day (90th percentile for women of childbearing age: USEPA, 2019); RSC-20%	3.6 ng/L (total of 4 PFAS)
California EPA (2021)	PFOA	CSF 0.0026 $(ng/kg/day)^{-1}$	Increased risk of kidney cancer (Vieira et al., 2013; Shearer et al., 2021)	0.03 L/kg/day (NJ default: 2.4 L/day, 80 kg body wt.); RSC -20%	0.012 (at 1 x 10^{-6} cancer risk level)
		Acceptable Daily Dose* 0.87 ng/kg/day	Increased risk of clinically defined elevated ALT (Gallo et al., 2012)		5.8
	PFOS	Acceptable Daily Dose* 0.64 ng/kg/day	Increase risk of clinically defined high cholesterol (Steenland et al., 2009)		4.3
National Academies of Sciences, Engineering, and Medicine (2022)	Total serum concentration of 7 PFAS***	>2 – 20 ng/ml. "a potential for adverse effects, especially in sensitive populations" Recommend reducing exposure if PFAS source(s) are known and use of home water filters when PFAS is elevated in drinking water.	German Human Biomonitoring (HBM) Level I for PFOA; based on serum levels associated with multiple human health effects (Hölzer et al., 2021)	Not applicable	
		>20 ng/ml "increased risk of adverse effects" Recommended specific clinical monitoring beyond the usual standard of care.	German Human Biomonitoring (HBM) Level I for PFOS; based on serum levels associated with multiple human health effects (Schümann et al., 2021).		

* EFSA Tolerable Daily Intakes and California EPA Acceptable Daily Doses are non-cancer toxicity factors analogous to USEPA and NJDEP RfDs.

** Health-based drinking water concentrations were developed by Health Effects Subcommittee.

** PFOA, PFOS, PFNA, PFHxS, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and methyl perfluorooctane sulfonamidoacetic acid (MeFOSAA)

REVIEW OF RECENT INFORMATION ON KEY HEALTH ENDPOINTS

Numerous peer-reviewed publications about health effects of PFOA, PFOS, and PFAS in general have become available since the Health Effects Subcommittee completed its evaluations of PFOA (DWQI, 2017a) and PFOS (DWQI, 2018). These include many additional studies reporting associations of health effects with PFOA and PFOS within the general population exposure range, some of which were included in the draft USEPA (2021a,b) PFOA and PFOS evaluations and others that were not. Additionally, recent laboratory animal studies demonstrate concordance with some of the health effects reported in humans. Overall, these newer studies provide further support for the use of human data in risk assessment of PFOA and PFOS.

The Subcommittee's detailed review of relevant health effects information is presented in Appendix 3 (page 45). For each of the four non-cancer endpoints with the most consistent epidemiological evidence for associations with PFOA and PFOS (decreased antibody response to vaccination; hepatic effects-increased serum ALT; decreased birth weight; increased serum lipids -cholesterol), the USEPA (2016a,b), DWQI (2017a, 2018), and USEPA (2021a,b) evaluations, as well as relevant USEPA SAB (2022) comments, are summarized. Additional key studies not included in these evaluations are also discussed when appropriate. The Subcommittee's review also included recent epidemiological evidence for cancer and PFOA, as well as a recent study of overall mortality and PFAS including PFOA and PFOS. Finally, the epidemiological evidence for impacts of PFAS on duration of breast feeding is reviewed since this is an important effect that has been consistently reported in multiple studies.

It is important to emphasize that the Subcommittee did not conduct a comprehensive review of all studies that have become available since the DWQI (2017a, 2018) completed its evaluations of PFOA and PFOS. A review of all of the numerous newer studies would be a massive undertaking that is beyond the scope of this Health Effects Subcommittee task.

CONSIDERATIONS RELEVANT TO EXPOSURE TO PFOA AND PFOS IN DRINKING WATER IN ADULTS AND INFANTS

Adults

PFOA and PFOS bioaccumulate in humans, and ongoing exposures to even relatively low drinking water concentrations of these PFAS result in substantial elevations in blood serum levels (DWQI 2017a; 2018; Post et al., 2012, 2017, 2021). The estimated increase in blood serum PFOA or PFOS levels from a given PFOA or PFOS concentration in drinking water can be predicted from the clearance factor (CL; L/kg/day), which is inversely proportional to the half-life (days) and proportional to the volume of distribution (L/kg)[5], and the drinking water ingestion rate (L/kg/day)[6] (DWQI, 2017a; 2018; Post et al., 2021).

[5] Clearance Factor (CL; L/kg/day) = Volume of Distribution (L/day) x (ln 2 /Half-life [days])

[6] Increase in Serum Conc. (µg/L) = (Drinking Water Conc. [µg/L] x Ingestion Rate [L/kg/day]/CL [L/kg/day])

Tables 2 and 3 and Figures 1 and 2 (below) show the predicted increases in serum PFOA and PFOS concentrations from ongoing ingestion of the drinking water concentrations at the Interim USEPA Health Advisories, NJ PQLs, and NJ MCLs. The predicted serum concentrations shown in these tables and figures are based on the clearance factors of 1.4×10^{-4} L/kg/day for PFOA and 8.1×10^{-5} L/kg/day for PFOS used by DWQI (2017a, 2018) and USEPA (2016a,b).[7] Increases in serum level are predicted for the mean U.S. drinking water ingestion rate of 0.016 L/kg/day (USEPA, 2011) and the upper percentile value of 0.030 L/kg/day (based on 90th percentile drinking water ingestion of 2.4 L/day and mean adult body weight of 80 kg) recommended by USEPA (2015) for use in development of health-based water criteria. In the tables and figures, the increased serum levels from drinking water are compared to the most recent median U.S. general population (NHANES, 2017-18) serum levels of 1.47 ng/ml for PFOA and 4.30 ng/ml for PFOS (CDC, 2022), which are assumed to result from non-drinking water exposures.

Table 2. Increase in serum PFOA concentrations predicted from various concentrations of PFOA in drinking water*

Drinking Water Conc. (ng/L)	Mean Water Ingestion Rate (0.016 L/kg/day)			Upper Percentile Water Ingestion Rate (0.030 L/kg/day)		
	Increase in serum (ng/ml)	Total serum** (ng/ml)	% increase from drinking water**	Increase in serum (ng/ml)	Total serum** (ng/ml)	% increase from drinking water**
0	0	1.47	0%	0	1.47	0%
6 (NJ PQL)	0.68	2.15	46%	1.28	2.75	87%
14 (NJ MCL)	1.60	3.07	109%	3.0	4.47	204%

* Predicted serum:drinking water ratios, based on clearance factor of 1.4×10^{-4} L/kg/day, are 114:1 at mean drinking water intake and 214:1 at upper percentile drinking water intake. Mean and upper percentile ingestion rates are from USEPA (2011) and USEPA (2015), respectively.

** Total serum concentrations and % increases from drinking water are based on assumption of 1.47 ng/ml in serum (U.S. median value from NHANES, 2017-18) from non-drinking water exposures.

[7] The half-lives used in the (DWQI, 2018, 2018)/USEPA (2016a,b) clearance factors are 2.3 years (Bartell et al., 2010) for PFOA and 5.4 years (Olsen et al., 2007) for PFOS. It is noted that USEPA (2021a,b) used a slightly higher half-life for PFOA (2.7 years; Li et al., 2018) and a lower half-life for PFOS (3.4 years; Li et al, 2018) than those used by DWQI (2017a, 2018)/USEPA (2016a,b); the volumes of distribution (0.17 L/kg for PFOA; 0.23 L/kg for PFOS from Thompson et al., 2010) were not changed. Use of the half-lives selected by USEPA (2021a,b) would result in somewhat greater increases in serum PFOA levels and somewhat smaller increases in serum PFOS levels than those shown in Tables 1 and 2 and Figures 1 and 2.

Table 3. Increase in serum PFOS concentrations predicted from various concentrations of PFOS in drinking water*

Drinking Water Conc. (ng/L)	Mean Water Ingestion Rate (0.016 L/kg/day)			Upper Percentile Water Ingestion Rate (0.030 L/kg/day)		
	Increase in serum (ng/ml)	Total serum** (ng/ml)	% increase from drinking water**	Increase in serum (ng/ml)	Total serum** (ng/ml)	% increase from drinking water**
0	0	4.30	0%	0	4.30	0%
4 (NJ PQL)	0.79	5.09	18%	1.48	5.78	34%
13 (NJ MCL)	2.56	6.86	60%	4.81	9.11	112%

* Predicted serum:drinking water ratios, based on clearance factor of 8.1 x 10^{-5} L/kg/day, are 197:1 at mean drinking water intake and 370:1 at upper percentile drinking water intake. Mean and upper percentile ingestion rates are from USEPA (2011) and USEPA (2015), respectively.

** Total predicted serum concentrations and % increases from drinking water are based on assumption of 4.30 ng/ml in serum (U.S. median value from NHANES, 2017-181-12) from non-drinking water exposures.

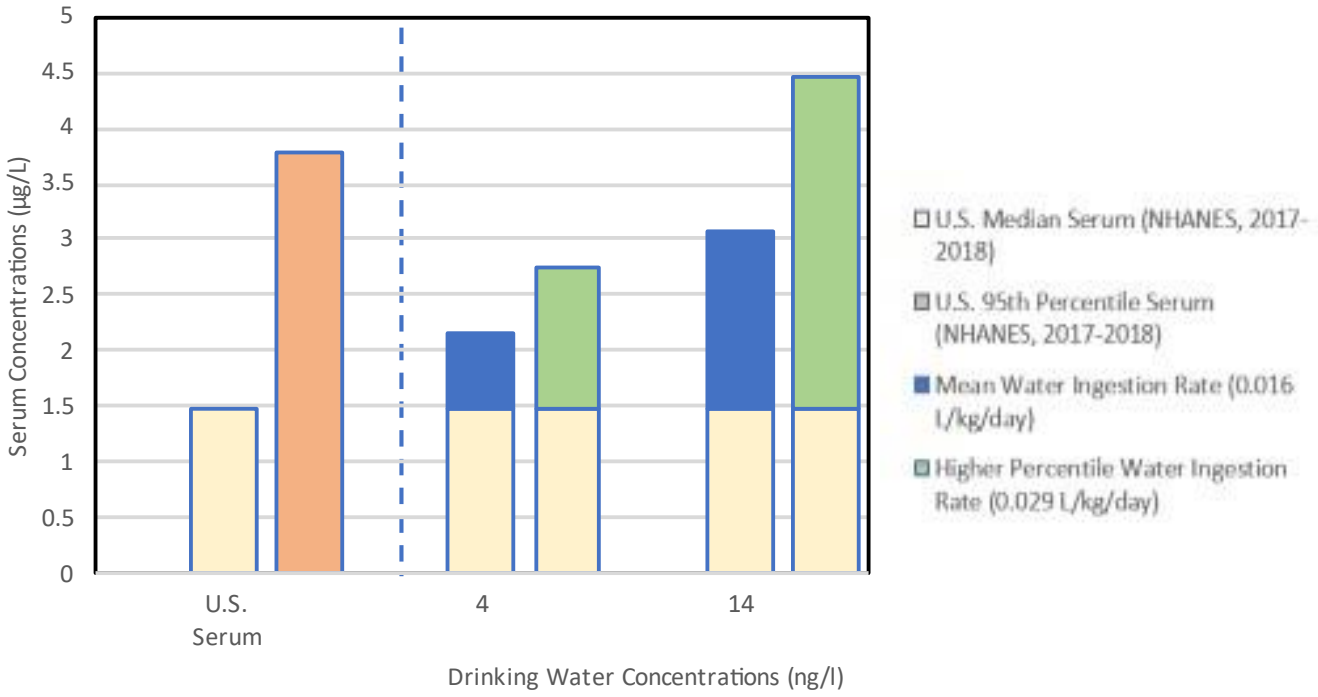

Figure 1. Increases in serum PFOA concentrations predicted from mean (0.016 L/kg/day; USEPA, 2011) and upper percentile (0.030 L/kg/day; USEPA, 2015) consumption of drinking water with various concentrations of PFOA, as compared to U.S median (1.47 ng/ml) and 95th percentile (3.77 ng/ml) serum PFOA levels (NHANES, 2017-18). Predicted serum:drinking water ratios, based on clearance factor of 1.4 x 10^{-4} L/kg/day, are 114:1 at mean drinking water intake and 214:1 at upper percentile drinking water intake.

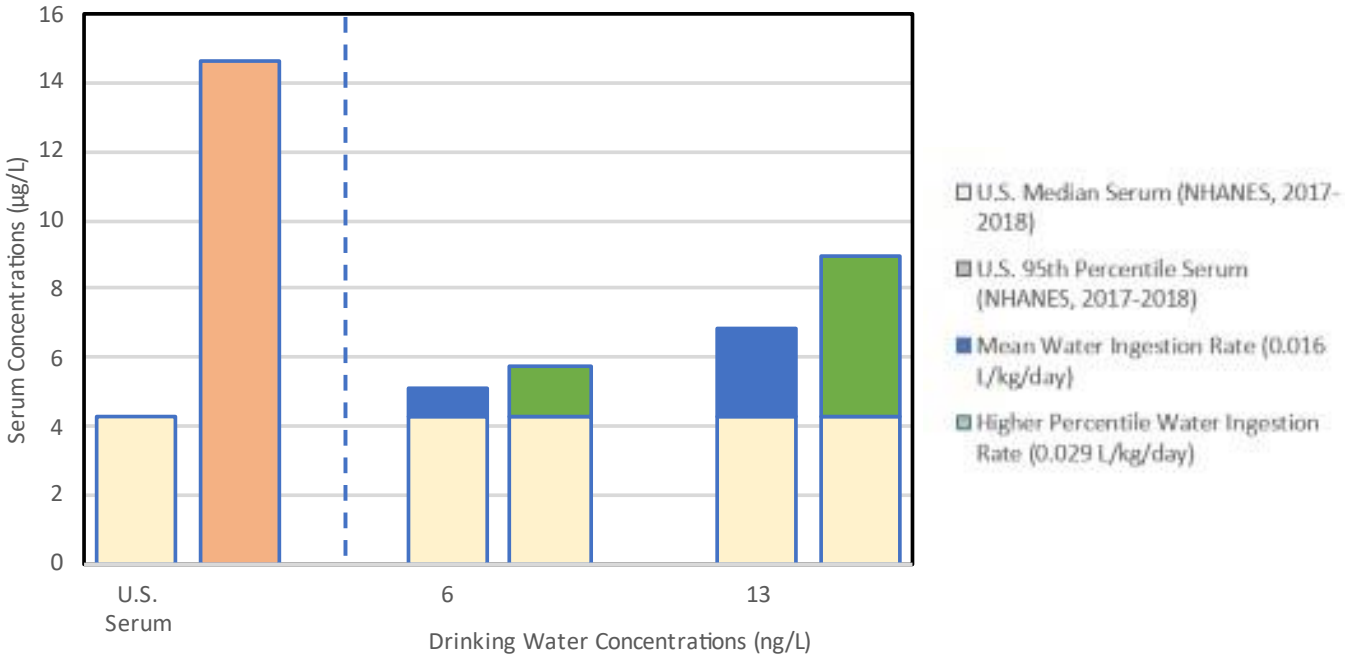

Figure 2. Increases in serum PFOS concentrations predicted from mean (0.016 L/kg/day; USEPA (2011) and upper percentile (0.030 L/kg/day; USEPA, 2015) consumption of drinking water with various concentrations of PFOS, as compared to U.S median (4.30 ng/ml) and 95th percentile (14.6 ng/ml) serum PFOS levels (NHANES, 2017-18). Predicted serum:drinking water ratios, based on clearance factor of 8.1 x 10^{-5} L/kg/day, are 197:1 at mean drinking water intake and 370:1 at upper percentile drinking water intake.

The serum PFOA and PFOS concentrations predicted to result from drinking water exposure can be compared to the serum-level PODs for the candidate RfDs proposed by USEPA (2021a,b). The predicted serum PFOA and PFOS concentrations can also be compared to serum-level candidate RfDs (called "Target Human Serum Levels" in DWQI, 2017a, 2018) by applying the uncertainty factor of 10 for intra-individual variability used by USEPA (2021a,b) to the serum-level PODs. See Table 4 below.

For PFOA, USEPA (2021a) presented one candidate RfD based on decreased vaccine response in children and five candidate RfDs based on five separate studies of decreased birth weight. For PFOS, USEPA (2021b) presented one candidate RfD based on decreased vaccine response in children and four candidate RfDs based on four separate studies of decreased birthweight.

Table 4. Serum-level PODs and serum-level RfDs* for candidate RfDs from USEPA (2021a,b)

	PFOA (USEPA, 2021a)		*PFOS (USEPA, 2021b)*	
Critical effect	Serum-level POD (ng/ml)	Serum-level RfD (ng/ml)	Serum-level POD (ng/ml)	Serum-level RfD (ng/ml)
Decreased vaccine response	0.17	0.017	0.54	0.054
Decreased birth weight	1.7, 1.8, 1.9, 2.1, 9 (5 studies)	0.17, 0.18, 0.19, 0.21, 0.9 (5 studies)	5.8, 7.6, 7.9, 41.2 (4 studies)	0.58, 0.76, 0.79, 4.12 (4 studies)

* Serum-level RfDs (called "Target Human Serum Levels" by DWQI, 2017a; 2018) were derived by applying the uncertainty factor of 10 for intra-individual variability used by USEPA (2021a,b) to the serum-level PODs presented by USEPA (2021a,b).

The serum-level PODs and RfDs in Table 4 can be compared to the serum PFOA and PFOS levels predicted to result from drinking water at the NJ PQL and MCL concentrations. For PFOA at the MCL of 14 ng/L, the serum levels of 3.1 ng/L and 4.5 ng/L predicted from average and upper percentile drinking water ingestion, respectively, are higher than 5 of the 6 serum-level PODs and all of the serum-level RfDs shown in Table 3. At the PFOA PQL of 6 ng/L, the predicted serum level from average ingestion of 2.75 ng/ml is higher than or very close to five of the six serum-level PODs and above all of the serum-level RfDs. For upper percentile ingestion at the PQL of 6 ng/L, the serum PFOA level of 4.5 ng/L is higher than five of the six serum-level PODs and all of the serum-level RfDs.

For PFOS at the MCL of 13 ng/L, the serum level of 6.9 ng/ml predicted from average drinking water ingestion is above or close to four of the five serum-level PODs and the serum level of 9.1 ng/L from upper percentile ingestion is above four of the five serum-level PODs and all of the serum-level RfDs. At the PFOS PQL of 4 ng/L, the predicted serum level of 5.1 ng/ml from average ingestion is close to four of the five serum-level PODs and at or above all of the serum-level RfDs, and the predicted serum level from upper percentile ingestion of 5.8 ng/ml is close to or above four of the five serum-level PODs and all of the serum-level RfDs.

While recognizing that USEPA (2022f) has stated that the draft RfDs for PFOA and PFOS are expected to change when finalized, the analysis provided above indicates that exposures to PFOA and PFOS in drinking water at the current NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS are close to or above most of the draft serum-level PODs for the candidate RfDs and above all of the serum-level RfDs presented by USEPA (2021a,b). This information further supports the conclusion that Health-based MCLs below the current NJ PQLs are appropriate.

Infants

A summary of this topic is presented below. Detailed information, including original analyses performed by the Health Effects Subcommittee analyses is provided in Appendix 4 (page 62).

Exposures to PFOA, PFOS, and other long-chain PFAS in breastfed infants are of concern both in the general population and in communities with contaminated drinking water (Lakind et al.,

2022; Post, 2022). As reviewed in Appendix 4, serum PFOA and PFOS levels in breastfed infants are similar or lower than in their mothers at birth and then increase by several-fold between birth and 6 months of age, with PFOA serum levels at age 6 months almost 4-fold higher than maternal serum levels. A recent study reported median concentrations of PFOA and PFOS at or above the New Jersey MCLs of 14 ng/L for PFOA and 13 ng/L in breast milk collected in 2019 from women from the general population (not known to be exposed to contaminated drinking water) in the Seattle area (Zheng et al., 2021; discussed in more detail in Appendix 4). These exposures are of concern because infants are a sensitive subpopulation for the developmental effects of PFOA and PFOS and for other effects of these PFAS that result from early life exposures, such as decreased antibody response to vaccines (Grandjean et al., 2012; Abraham et al., 2020).

When drinking water is contaminated with PFOA and/or PFOS, exposures to both breastfed infants and infants who consume formula prepared with contaminated drinking water are higher than in older individuals. This is the case because infants ingest more fluid (breast milk or formula) on a body weight basis than older individuals. Importantly, exposures resulting from contaminated drinking water are much higher in breastfed infants than in formula-fed infants because concentrations of PFOA and PFOS in breast milk are higher than in the mother's drinking water, with higher predicted breast milk:drinking water ratios (8.3:1 - 9.1:1) for PFOA (Post, 2022). Detailed information and numerical analyses are provided in Appendix 4.

The Health Effects Subcommittee recognized the higher PFOA exposures in infants, particularly those that are breastfed, in its early work including in its 2010 internal draft Health-based MCL Support Document (DWQI Health Effects Subcommittee, 2010a) and in a peer-reviewed publication by current Subcommittee members (Post, Cohn, Cooper, 2012). When developing Health-based MCLs for PFOA and PFOS, the Health Effects Subcommittee (DWQI, 2017a, 2018) emphasized concerns about potential adverse effects from the higher exposure to infants, particularly those that are breastfed. However, at the time when the DWQI Health-based MCLs were developed, models for quantitatively considering PFOA and PFOS exposure to the breastfed infant were not yet available.

After the Health Effects Subcommittee had completed its development of Health-based MCLs for PFOA and PFOS, a transgenerational toxicokinetic model to predict early-life exposures to PFAS from contaminated drinking water was developed by the Minnesota Department of Health and published in a peer-reviewed journal (Goeden et al. 2019). This model considers transplacental exposure to the fetus resulting from maternal consumption of PFAS-contaminated drinking water, exposure from birth until age one year via breast milk or formula prepared with PFAS-contaminated water, and continued exposure from PFAS-contaminated water from early childhood through adulthood (Figure 3). For example, peak serum PFOA levels in breastfed infants resulting from maternal consumption of PFOA in drinking water are predicted to be six times higher than in adults who consume water with the same PFOA concentration.

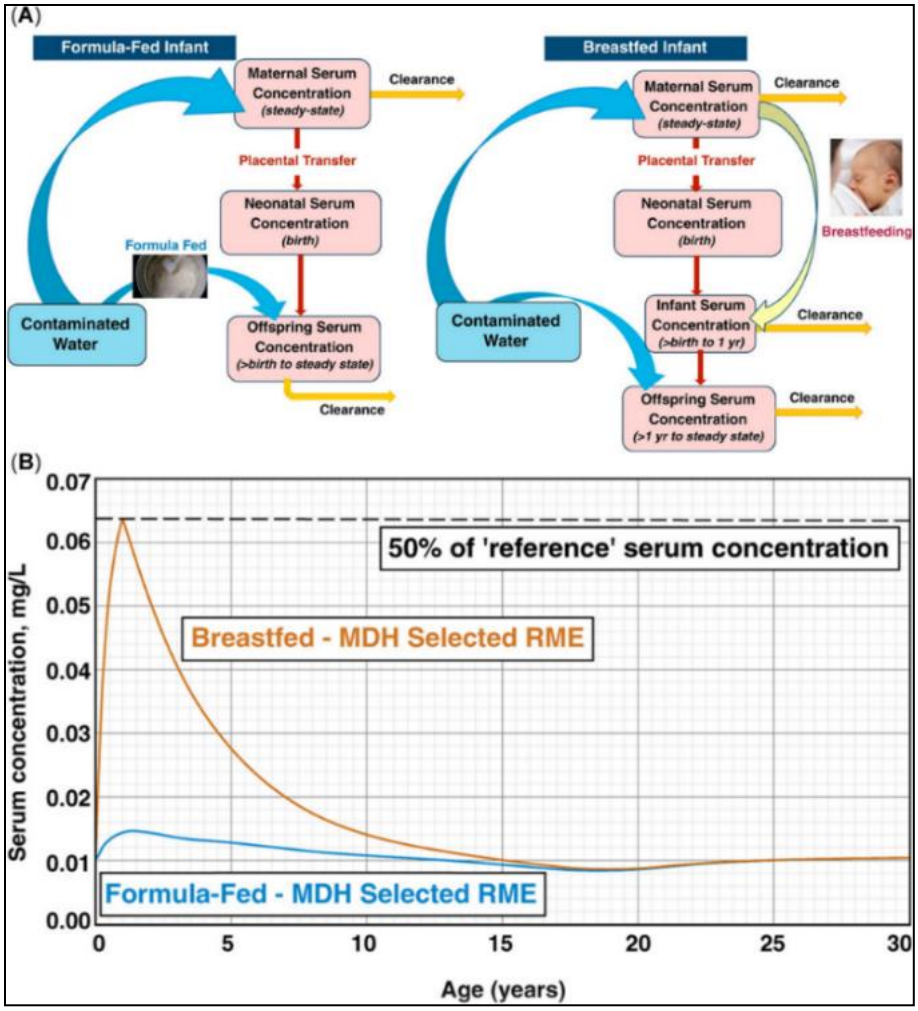

Figure 3. Toxicokinetic model for transgenerational to PFOA from drinking water. (A) Conceptual representation of the model for formula-fed and breastfed infant exposure scenarios. (B) Predicted serum levels from drinking water at the Minnesota guideline level of 35 ng/L. MDH=Minnesota Department of Health; RME=reasonable maximum exposed (Goeden et al. 2019).

USEPA (2021a,b) also considered the higher exposures to breastfed infants for development of PODs for effects caused by prenatal and/or early life exposure using a model developed by Verner et al. (2016). USEPA SAB (2022) strongly supported use of a model to consider prenatal and early life exposure. However, it questioned whether the Verner et al. (2016) model is appropriate for development of health-based drinking water levels (e.g., MCLGs) and recommended that USEPA consider using Goeden et al. (2019) model because it was "not clear how a RfD from the Verner et al. (2016) model, which predicts serum PFOA or PFOS levels at age 5 years from a constant daily dose to the mother and the child, can be used to develop an MCLG that considers both exposure through breastfeeding, post-weaning and changing drinking water consumption rates up to age 5. In contrast, the Goeden et al. (2019) model considers both age-specific toxicokinetic factors and the changing drinking water intakes at different age periods [e.g., maternal, infant, children of different ages] … and predicts the serum PFOA or

PFOS levels at any age (including infancy, childhood, and adulthood) that result from maternal and child consumption of drinking water with a certain concentration (ng/L) of PFOA or PFOS."

The Goeden et al. (2019) model has been used, along with state-specific RfDs, by Minnesota and at least three other states (Michigan, New Hampshire, and Washington) to develop health-based drinking water standards for PFOA and PFOS (reviewed in Post, 2021). It is noted that the health-based drinking water standards developed with the Goeden et al. (2019) model have used an infant-specific RSC of 50% that is 2.5-fold less stringent (i.e., resulting in a 2.5-fold higher drinking water value) than the default RSC of 20% used by DWQI (2017a, 2018). All other factors (e.g., RfDs, clearance factor) being equal, health-based drinking water concentrations developed with the Goeden et al. (2019) model are lower than with the default approach of a constant drinking water ingestion rate.

Health-based MCLs using the Goeden et al. (2019) model (including an RSC of 50%) with the RfDs (2 ng/kg/day for PFOA; 1.8 ng/kg/day for PFOS) and clearance factors from DWQI (2017a, 2018) are estimated as 3.9 ng/L for PFOA, slightly below the New Jersey PQL of 6 ng/L, and 11 ng/L for PFOS, somewhat above the New Jersey PQL of 4 ng/L for PFOS. Use of lower RfDs based on human data would result in even lower Health-based MCLs. These estimated Health-based MCLs that consider exposure to breastfed infants further support the conclusion that Health-based MCLs below the NJ PQLs are appropriate.

In an analysis presented in Appendix 4, the Health Effect Subcommittee compared peak serum PFOA concentrations in breastfed infants (Goeden et al., 2019) at several drinking water concentrations to the range of No Observed Adverse Effect Concentration (NOAEC) serum PFOA levels (12.2 to 16.9 ng/ml) for decreased antibody response to three different vaccines in one year old children (Abraham et al., 2020)[8]. Serum PFOA concentrations in infants whose mothers consume drinking water with 14 ng/L PFOA at an average ingestion rate were predicted to exceed the NOAECs for decreased vaccine response and to greatly exceed RfDs that could be derived from these NOAECs by application of 10-fold uncertainty factor for inter-individual variability. This analysis provides further support for a Health-based MCL for PFOA below the New Jersey PQL of 6 ng/L.

In summary, the data reviewed above show that levels of PFOA and PFOS in breast milk at levels are above the New Jersey Health-based MCLs even in the absence of contaminated drinking water. Furthermore, concentrations of these PFAS in breast milk are much higher when drinking water is contaminated. These data indicate that exposure to PFOA and PFOS in drinking water should be minimized, partcularly because infants are a susceptible subpopulation for effects of these PFAS. This information further supports the conclusion that Health-based MCLs for PFOA and PFOS should be below the NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

[8] It should be noted that this analysis is intended as an example, and that it is based serum-level NOAECs for PFOA from Abraham et al. (2020) because the required data were provided in the publications, not because the NOAECs from this study are necessarily the most sensitive effects of PFOA.

CONSIDERATION OF RISKS OF PFAS MIXTURES

Potential toxicological interactions of multiple PFAS that co-occur in drinking water are relevant to the discussion of whether current scientific information supports Health-based MCLs below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS. This section provides an overview of this topic, and a detailed discussion is found in Appendix 5 (page 71).

USEPA developed a draft document on potential approaches for the evaluation of risks of PFAS mixtures (USEPA, 2021c) as part of its overall effort to regulate PFOA and PFOS in drinking water, and this document was reviewed by USEPA SAB (2022). In addition, at least four states (Maine, Massachusetts, Oregon, Vermont) have established drinking water guidelines based on the total concentration of multiple (four to six) PFAS (ITRC 2022a), and at least one other state (Minnesota) assumes dose additivity for contaminants (including PFAS and others) that cause the same general toxicological effect (MDH, 2020). The European Union and some European nations have also developed drinking water guidelines for mixtures of PFAS (ITRC, 2022a). When PFAS co-occur, consideration of toxicological interaction of mixtures decreases the maximum allowable levels of any one compound.

As reviewed in Appendix 5, experimental data on the toxicity of defined PFAS mixtures is extremely limited. Proposed approaches for addressing risks of PFAS mixtures (reviewed in Appendix 5) include the total concentration (simple additive) approach, the Hazard Index approach, and the Relative Potency Factor approach.

Health-based MCLs developed by the Health Effects Subcommittee (DWQI, 2015, 2017a, 2018) for PFNA, PFOA, and PFOS were based on consideration of health risks of each compound individually. A primary reason for the decision not to consider toxicological interactions of PFAS mixtures when developing the Health-based MCLs was the desire for consistency with the approach used for Health-based MCLs for other contaminants that were previously developed by the Subcommittee. Although toxicological interactions were not considered quantitatively, the Subcommittee acknowledged the potential for additive toxicity of PFAS that co-occur in drinking water as an uncertainty in its assessments.

The USEPA (2021c) draft framework for assessment of risks of non-carcinogenic effects of PFAS mixtures is based on the assumption of dose additivity for PFAS with a common health outcome (e.g., toxicological effect) without the requirement that the effect is known to occur through a common mode of action (MOA). The scientific basis and additional details of the draft framework are discussed in Appendix 5. USEPA SAB (2022) agreed with the USEPA (2021c) assumption of dose additivity based on a common health outcome (e.g., toxicological effect) as a health protective default approach for assessment of risks of PFAS mixtures and agreed with USEPA (2021c) that identification of a common MOA is not required.

Conley et al. (2022) study of effects of co-exposure to PFOA and PFOS during gestation in rats

A recent study from the USEPA Office of Research and Development toxicology laboratories (Conley et al., 2022) evaluated maternal and offspring effects in dams dosed on gestation day

(GD) 8 through postnatal day (PND) 2 with PFOA, or a mixture of PFOS (2 mg/kg/day) and varying doses of PFOA; this study is discussed in detail in Appendix 5. In summary, numerous toxicological endpoints were evaluated both in the dams and in the offspring. Concentrations of PFOA and PFOS in serum and liver from the same administered dose were not significantly different from co-exposure as compared to exposure to the individual compounds. Co-exposure to PFOS (2 mg/kg/day) shifted the dose-response curve for PFOA for many but not all maternal and pup endpoints such that the effects of a given dose of PFOA was greater than without co-exposure to PFOS. Dose additivity adequately described the interaction of PFOA and PFOS for most endpoints for which dose additivity and response additivity could be modeled. The authors concluded that their results "support the hypothesis of cumulative effects on shared endpoints from PFOA and PFOS co-exposure and dose additive approaches for predictive estimates of mixture effects."

The information reviewed above and in Appendix 5 supports consideration of toxicological interactions of PFAS that co-occur in drinking water. The focus of the evaluation presented herein is whether Health-based MCLs for PFOA and PFOS below the current NJ PQLs are supported by current scientific information. Therefore, the scope of this evaluation does not include recommendation of a specific approach for consideration of risks of PFAS mixtures. That being said, recognition that the toxicological effects of PFOA, PFOS, and/or other PFAS that co-occur in drinking water are likely to be additive or synergistic (greater than additive) supports more stringent Health-based MCLs than if such interactions were not considered. Therefore, the information discussed above provides additional support for NJ Health-based MCLs for PFOA and PFOS that are lower than current values.

HEALTH EFFECTS SUBCOMMITTEE CONCLUSIONS

The focus of the Health Effects Subcommittee's evaluation was to determine whether Health-based MCLs below the New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS are supported by current scientific information. To evaluate this issue, the Subcommittee reviewed the interim USEPA (2022a,b) Health Advisories and draft USEPA (2021a,b) health effects assessments for PFOA and PFOS, the USEPA SAB (2022) review of the draft USEPA (2021a,b) health effects assessments, and other relevant information including key recent peer-reviewed publications, recent PFOA and PFOS evaluations based on human data by other authoritative organizations, the USEPA (2021c) draft document on approaches for risk assessment of per- and polyfluoroalkyl substances (PFAS) mixtures, and previous Subcommittee conclusions on health effects and risk assessment of PFAS.

The Subcommittee emphasizes that the current Health-based MCLs of 14 ng/L for PFOA (DWQI, 2017a) and 13 ng/L for PFOS (DWQI, 2018) were determined to be public health protective and scientifically supportable based on the information available at the time when they were developed. It also notes that several other states used the Subcommittee's conclusions in developing their own PFOA and PFOS drinking water guidelines (Post, 2021). However, as described below, the Subcommittee concluded that multiple lines of evidence indicate that

Health-based MCLs below the current NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS are supported by current scientific information.

The Subcommittee agrees with the major conclusions (described below) of the USEPA (2021a,b) toxicity assessments that provide the scientific basis for the interim USEPA (2022a,b) Health Advisories for PFOA and PFOS. The Subcommittee also notes that USEPA SAB (2022) generally agreed with the USEPA (2021a,b) toxicity assessments' major conclusions. It further notes that several of these major conclusions are consistent with conclusions of the Subcommittee's earlier reports (internal draft PFOA Health-based MCL Support Document, DWQI Health Effects Subcommittee, 2010a; DWQI, 2017a; DWQI, 2018) and peer-reviewed publications by its members (e.g., Post, Cohn, Cooper, 2012; Post, Gleason, Cooper, 2017; Post, 2022).

The Subcommittee's review of USEPA (2021a,b; 2022a,b), USEPA SAB (2022), and other relevant information indicates that multiple lines of evidence support the conclusion that Health-based MCLs below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS are scientifically supportable, as follows:

- **The Subcommittee concludes that human data are appropriate for RfD development for PFOA and PFOS.** Health-based MCLs for PFOA and PFOS based on RfDs from human data from multiple studies and endpoints reviewed above are consistently very close to or below the New Jersey PQLs. This is true for Health-based MCLs developed both from the range of PFOA and PFOS POD_{HED} values and from potential RfDs from human studies from USEPA (2021a,b). It is also true for Health-based MCLs using the non-cancer toxicity factors from human studies that were proposed by California EPA (2021) for PFOA and PFOS and the non-cancer toxicity factor from human data adopted by EFSA (2020) for the total of PFOA, PFOS, and two other PFAS.

- **The Subcommittee concludes that increased risk of human kidney cancer is an appropriate basis for a CSF for PFOA.** A Health-based MCL for PFOA based on a cancer slope factor for increased risk of human kidney cancer and the one in one million (10^{-6}) cancer risk level will be far below the New Jersey PQL of 6 ng/L, regardless of which study or studies of human kidney cancer and PFOA are selected as the basis for the cancer slope factor.

- The Subcommittee concludes that previous evaluations by the Health Effects Subcommittee (DWQI, 2017a) and its members (Post, Cohn, Cooper, 2012) indicate that **low dose developmental effects of PFOA in laboratory animals (e.g., delayed mammary gland development in mice) support a Health-based MCL for PFOA below the New Jersey PQL of 6 ng/L.**

- The Subcommittee concludes that **infants are a susceptible subpopulation for adverse effects of PFOA and PFOS and that the higher PFOA and PFOS exposures to infants,**

particularly those who are breastfed, support Health-based MCLs below the New Jersey PQLs. It is noted that use of a toxicokinetic model that considers exposure to PFAS through breastmilk results in lower health-based drinking water levels even when the current RfDs based on animal data are used, including a health-based drinking water level for PFOA below the current PQL of 6 ng/L. Use of the toxicokinetic model with the lower RfDs based on human data would result in even lower Health-based MCLs.

- Relevant to the conclusions about infant exposures above, **the Subcommittee further notes that PFOA and PFOS were detected in breast milk at median concentrations at or above the New Jersey Health-based MCLs in a recent study of women from the U.S. general population with little or no drinking water exposure.** The results of this study and other recent studies of PFOA and PFOS concentrations in breast milk support the conclusion that exposure to PFOA and PFOS in drinking water should be minimized to the greatest extent that is feasible.

- **The Subcommittee notes that PFOA, PFOS, and other PFAS typically occur in drinking water as mixtures and that it is important to consider toxicological interactions of PFAS that co-occur in drinking water.** The Subcommittee agrees with USEPA (2021c) and USEPA SAB (2022) that dose additivity is an appropriate and health-protective default assumption for assessing the non-cancer risks of PFAS mixtures, in the absence of chemical-specific data. Although a quantitative assessment of the risks of PFAS mixtures was outside of the scope of the Subcommittee's evaluation, the Subcommittee concludes that consideration of toxicological interactions of PFAS that co-occur in drinking water supports more stringent Health-based MCLs for PFOA and PFOS.

- Finally, the Subcommittee notes that several conclusions of earlier Subcommittee evaluations, including the relationship between administered dose and serum PFOA/PFOS levels and the importance of exposure to infants through breast milk, were accepted by USEPA (2021a,b) in its recent evaluations. The Subcommittee also notes that the more recent information reviewed in this current evaluation provides further support for the Subcommittee's earlier conclusions.

Specifically, the Subcommittee agrees with the following conclusions from USEPA (2021a,b; 2022a,b) and USEPA SAB (2022):

- As above, the Subcommittee agrees with USEPA (2021a,b; 2022a,b) and USEPA SAB (2022) that **human data are appropriate for use as the basis for non-cancer RfDs for PFOA and PFOS and a CSF for PFOA.** It is noted that the use of human data is supported by numerous more recent epidemiological studies demonstrating associations of health effects and PFOA and/or PFOS that were identified by USEPA (2021a,b), USEPA SAB (2022), and the Subcommittee, but were not available to DWQI (2017a, 2018).

- The Subcommittee agrees with USEPA (2021a, b) and USEPA SAB (2022) that the **health endpoints with the strongest human evidence for PFOA and PFOS are increased serum cholesterol, decreased antibody response to vaccination, decreased fetal growth (i.e., birth weight), increased serum ALT, and, for PFOA, increased risk of kidney cancer**. The Subcommittee notes that the large majority of epidemiological studies reporting associations of non-cancer effects and PFOA and/or PFOS are from the general population with no known drinking water exposure. Similarly, there is evidence for increased risk of kidney cancer from exposure to PFOA within the general population as well as in communities with elevated exposure from contaminated drinking water. Additionally, the Subcommittee concludes that there is consistent evidence for negative impacts of PFOA and PFOS on lactational function (e.g., decreased duration of breastfeeding) within the general population exposure range.

- The Subcommittee agrees with USEPA (2021a,b) and USEPA SAB (2022) that available scientific information supports the conclusion that **PFOA is "*Likely to Be Carcinogenic to Humans*" and that PFOS has *"Suggestive Evidence of Carcinogenic Potential."***

- For health endpoints resulting from chronic exposure, the Subcommittee agrees with USEPA (2021a,b; 2022a,b) and USEPA SAB (2022) that **a clearance factor (ml/kg/day) should be used to relate external exposures (ng/kg/day) of PFOA and PFOS to internal doses** as indicated by steady-state serum levels (ng/ml).

- For health endpoints resulting from prenatal and/or early life exposure, the Subcommittee agrees with USEPA (2021a,b; 2022a,b) and USEPA SAB (2022) that **a transgenerational toxicokinetic model that considers prenatal exposure and the higher exposures of infants, particularly those who are breastfed, should be used to predict exposures** to PFOA and PFOS from drinking water at various life stages.

APPENDIX 1: PREVIOUS EVALUATIONS BY HEALTH EFFECTS SUBCOMMITTEE AND ITS MEMBERS

This Appendix reviews previous evaluations by the Health Effects Subcommittee and its members that are relevant to the current Subcommittee evaluation. The Health-based MCL Support Documents that recommended Health-based MCLs of 13 ng/L for PFNA (DWQI, 2015), 14 ng/L for PFOA (DWQI, 2017), and 13 ng/L for PFOS (DWQI, 2018) were written by the Subcommittee in response to the April 21, 2014 request from NJDEP Commissioner Bob Martin for the DWQI to recommend MCLs for PFNA, PFOA, and PFOS, in that order (discussed in DWQI, 2015). However, it is important to note that the Subcommittee extensively evaluated PFOA and other PFAS as emerging drinking water contaminants long before the 2014 request from Commissioner Martin. The chronology of the earlier NJDEP and DWQI work on perfluorinated chemicals (PFCs; the term used for PFAS at the time) was presented (Post, 2014) on May 29, 2014, when the DWQI was reconvened to address the Commissioner's request to develop MCLs for the three PFAS.

As discussed in detail below, the Health Effects Subcommittee first concluded that PFOA bioaccumulates from drinking water in humans, that PFOA exposures within the general population range are associated with multiple human health effects, that low doses of PFOA cause toxicity in laboratory animals, that PFAS exposures in breastfed infants are much higher than in older individuals, and that low concentrations of PFOA and other PFAS are of concern in 2009-2010, well before this information and these conclusions were widely acknowledged or accepted by other regulatory authorities or the general scientific community. These conclusions are now widely accepted and most or all of them are used as the basis of drinking water guidelines developed by other states (reviewed in Post, 2021) and/or USEPA (2021a,b; 2022a,b). The more recent information reviewed in the current Subcommittee evaluation presented in this document provides further support for these earlier Subcommittee conclusions.

Post et al. (2009)

Post et al. (2009), entitled *"Occurrence and potential significance of perfluorooctanoic acid (PFOA) detected in New Jersey public drinking water systems,"* was published in the peer-reviewed journal Environmental Science & Technology. Its authors include two current members of the Health Effects Subcommittee (G. Post and K. Cooper). This publication presents the results of the 2006 statewide study of the occurrence of PFOA in public water systems conducted by NJDEP and the basis of the NJDEP (2007) chronic drinking water guidance PFOA of 40 ng/L which was much lower than other state and USEPA PFOA drinking water guidelines at the time (Post, 2021; Figure 1). Notably, the NJDEP (2007) guidance was the first PFAS drinking water guideline to consider the bioaccumulation of PFOA/PFAS from drinking water and one of the first to consider the longer half-life of PFAS in humans as compared to laboratory animals.

Relevant to the current Health Effects Subcommittee evaluation, Post et al. (2009) noted that data had recently become available that indicated associations of low serum PFOA levels with several human health effects. These data included preliminary results from the C8 Health Study reporting associations of increased serum cholesterol with serum PFOA levels within the range

prevalent in the U.S. general population at that time (i.e., 2003-2004 NHANES), as well as data from recent peer-reviewed publications reporting associations of PFOA with decreased fetal growth, increased time to pregnancy, and decreased normal sperm count in the general population. Post et al. (2009) noted that some of these human health effects were associated with serum PFOA levels below the Target Human Serum Levels (RfDs in terms of serum levels rather than external doses) based on animal toxicology data that were used as the basis of the NJDEP guidance of 40 ng/L.

DWQI Health Effects Subcommittee (2010a) internal draft Health-based MCL Support Document for PFOA

After the DWQI voted to add PFOA to its Workplan for MCL development in January 2009 (DWQI, 2009), the Health Effects Subcommittee began work on a draft Health-based MCL Support Document for PFOA. An internal draft of this document (DWQI Health Effects Subcommittee, 2010a) that was drafted by three current members of the Subcommittee (G. Post, P. Cohn, K. Cooper) with review and input from a fourth current member (J. Klotz) concluded that data from both human epidemiology studies and animal toxicology studies demonstrate that PFOA causes health effects within the general population exposure range, indicating that exposure from drinking water should be minimized.

Regarding human studies, DWQI Health Effects Subcommittee (2010a) states:

> "The epidemiological data indicates that multiple endpoints, including some considered adverse, are associated with PFOA exposure in occupational, contaminated drinking water, and/or general population studies; some of these findings are consistent with data from animal studies. Although causality for these effects has not been established (as is the case for most epidemiology studies), these associations occur at the lowest exposure levels studied, including within the range of exposure of the general population, with no apparent threshold in the dose-response curve"

Regarding human and animal studies, DWQI Health Effects Subcommittee (2010a) further states:

> "Although causality has not been proven, exposure to PFOA has been associated with many health endpoints [in human studies]. For some of these effects, the slope of the dose-response curve appears steepest within the exposure range of the general population. Current animal data reveals effects of concern at very low doses, with no NOAEL identified. Much of the data from humans and animals is very recent, and additional findings are constantly emerging."

Regarding the Target Human Serum Level, which was based on data from animal studies, the internal draft document states:

> "As discussed above, the Target Human Serum Level [based on data from animal studies], analogous to a Reference Dose, which is the basis for the recommended Health-based MCL is within the range of serum levels prevalent in the U.S. general population. This implies that a significant portion of the general population already exceeds the

health-based exposure level for this endpoint, and that any additional exposure should be minimized."

DWQI Health Effects Subcommittee (2010a), which is dated October 2010, also noted that Fromme et al. (2010) had very recently (August 2010) reported that serum PFOA levels in breastfed infants from the general population increased rapidly after birth and that serum PFOA levels at age 6 months were several times higher than in maternal serum.

September 10, 2010 memorandum from Health Effects Subcommittee to Testing and Treatment Subcommittees

As discussed in the minutes of the September 10, 2010 DWQI meeting (DWQI, 2010b), a memorandum (DWQI, 2010c) dated September 10, 2010 from the chair of the Health Effects Subcommittee to the chairs of the Testing and Treatment Subcommittees provided information on the Subcommittee's progress in developing a Health-based MCL for PFOA. The memorandum stated that the Subcommittee was considering potential Health-based MCLs for PFOA of 0.01- 0.04 μg/L (10-40 ng/L) or as low as reasonably achievable. In the memorandum, the Subcommittee recommended that the Testing and Treatment Subcommittees begin to "identify analytical and treatment information that might affect achieving HBMCLs [Health-based MCLs] within this general range."

Although the memorandum did not include the detailed basis for these recommendations, the potential Health-based MCLs mentioned in the memorandum were based on three options identified in DWQI Health Effects Subcommittee (2010a), as follows:

- The first option, a Health-based MCL of 10 ng/L, was based on the traditional approach of developing an RfD from the most sensitive toxicological effect from animal studies that is well established, adverse or a precursor to an adverse effect, and relevant to humans. The potential Health-based MCL of 10 ng/L was derived from a Target Human Serum Level of 7 ng/ml based on delayed mammary gland development in mouse offspring in a cross-fostering study (White et al., 2009). It was noted in the draft document that a subsequent study from the same research group that was in press at the time (Macon et al., 2011) reported delayed mammary gland development in mouse offspring at doses below those used in White et al. (2009); this study was evaluated in the final (DWQI, 2017) Health-based MCL Support Document (see *2017 Health-based MCL Support Document* below).
- The second option was a Health-based MCL that is "as low as possible based on analytical and treatment considerations" (noting that analytical Reporting Levels in drinking water at the time were 4-5 ng/L) because "a significant portion of the U.S. general population exceeds the health-based goal, and that additional exposure from drinking water should be minimized." Relevant to this option, DWQI Health Effects Subcommittee (2010a) discusses several health endpoints associated with serum PFOA levels within the general population range in epidemiology studies.
- The third option, which was included because "minimizing exposure to the greatest extent possible may not be feasible," was to set the Health-based MCL "at a level which will result

in a defined increase in exposure over the general population background level." For example, it was stated that "a drinking water concentration of 0.04 ug/L [40 ng/L] would increase serum levels by about 4 ng/ml, or a 100% increase (doubling) from the median [NHANES] serum level of 4 ng/ml [in 2010] to 8 ng/ml."

Post, Cohn, Cooper (2012)

A review paper entitled "*PFOA as an emerging drinking water contaminant: a critical review of recent literature,*" whose authors are current members of the Health Effects Subcommittee (P. Cohn, K. Cooper, G. Post), was published in the peer-reviewed journal Environmental Research in 2012. This publication comprehensively reviewed the available information on health effects and toxicokinetics of PFOA in humans and laboratory animals as well as information on other relevant topics such as occurrence, sources and uses, human exposure, and fate and transport. Post, Cohn, Cooper (2012) includes many of the conclusions presented in the earlier internal draft Subcommittee document (DWQI Health Effects Subcommittee, 2010a), and it reviewed the substantial amount of additional information that had become available since the draft document was written in 2010.

The abstract of Post, Cohn, Cooper (2012) states that "drinking water can substantially increase total human exposure, with a serum:drinking water ratio of about 100:1. For example, ongoing exposures to drinking water concentrations of 10ng/L, 40ng/L, 100ng/L, or 400 ng/L are expected to increase mean serum levels by about 25%, 100%, 250%, and 1000%, respectively, from the general population background serum level of about 4ng/mL. Infants are potentially a sensitive sub-population for PFOA's developmental effects, and their exposure through breast milk from mothers who use contaminated drinking water and/or from formula prepared with contaminated drinking water is higher than in adults exposed to the same drinking water concentration. Numerous health endpoints are associated with human PFOA exposure in the general population, communities with contaminated drinking water, and workers." The abstract further states that "…exposure to an environmentally relevant drinking water concentration caused adverse effects on mammary gland development in mice…"; a BMDL for this effect was developed within the paper.

In summary, Post, Cohn, Cooper (2012) concluded that: "Unlike most other well-studied drinking water contaminants, the human dose-response curve for several effects [of PFOA] appears to be steepest at the lower exposure levels, including the general population range, with no apparent threshold for some endpoints."

Final Health-based MCL Support Documents for PFOA and PFOS (DWQI, 2017, 2018)

The Subcommittee's Health-based MCL Support Documents for PFOA and PFOS (DWQI, 2017, 2018) include comprehensive critical reviews of the scientific literature relevant to toxicokinetics and health effects of these PFAS. DWQI (2017, 2018) concluded that PFOA and PFOS are associated with several human health effects within the general population exposure range even without additional exposure from drinking water, with evidence supporting criteria for causality for some endpoints. The documents also emphasize that exposure to low drinking water concentrations of PFOA and PFOS substantially increases human serum levels, that the elevated serum PFOA and PFOS levels persist for many years after drinking water exposure

ends, that exposures to infants are of particular concern but that it was not possible to fully consider the higher exposures to breastfed infants in development of the Health-based MCLs, and that potential additive effects of PFAS that co-occur in drinking water were not considered.

For PFOA, the Target Human Serum Level of 0.8 ng/L and associated RfD of 0.11 ng/kg/day for delayed mammary gland development in mice were below the average exposure levels in the general population, and some other toxicological effects in animals were reported at similarly low doses. This Target Human Serum Level and RfD were based on the BMDL for delayed mammary gland development from Macon et al. (2011) published in Post, Cohn, Cooper (2012).

DWQI (2017) stated that the Health-based MCL based on this RfD, using default adult exposure assumptions, would be 0.88 ng/L, which is far below the current NJ PQL of 6 ng/L. Although delayed mammary gland development was determined to be well established, adverse, and relevant to humans, it was not selected as the primary basis for the Health-based MCL because of lack of precedent for its use as the primary basis for risk assessment. Instead, an additional uncertainty factor to account for this and other potentially more sensitive effects was applied in development of the Reference Dose of 2 ng/kg/day based on increased relative liver weight.

For PFOS (DWQI, 2018), the RfD of 1.8 ng/kg/day is based on a Target Human Serum Level of 22.5 ng/L for decreased immune response (decreased plaque forming cell response) in mice (Dong et al., 2009). This Target Human Serum Level is very close to the upper percentiles of the general population exposure range at the time it was developed (e.g., 95th percentile serum PFOS level from NHANES 2013-14: 18.5 ng/ml, 95% confidence interval: 15.4-22.0 ng/ml).

Based on the information summarized above, the Health Effects Subcommittee (DWQI, 2017, 2018) concluded that "additional exposure [to PFOA or PFOS] from drinking water may potentially pose some risk of health effects. For this reason, it could not be definitively concluded that lifetime exposure to … [the Health-based MCLs of 14 ng/L for PFOA and 13 ng/L for PFOS] is protective of sensitive subpopulations with a margin of exposure."

DWQI (2017, 2018) also include comparisons of the basis of the DWQI Health-based MCLs and the USEPA (2016a,b) PFOA and PFOS Health Advisories. These comparisons discuss that USEPA (2016a,b) disagreed with several important conclusions that were determined to be scientifically supportable by DWQI (2017, 2018). Example of DWQI (2017, 2018) conclusions that were not accepted by USEPA (2016a,b) include that serum PFOA/PFOS levels prevalent in the general population can be related to external exposures with a clearance factor, that the increase in serum PFOA/ PFOS levels resulting from drinking water exposure can be predicted with a clearance factor and daily drinking water ingestion rates, that immune system suppression in mice is an appropriate and sensitive basis for a PFOS RfD, and that the much longer half-life of PFOA in humans than rats should be considered in developing a CSF for PFOA from chronic rat data. The Subcommittee notes that the current USEPA (2021a,b) health effects assessments of PFOA and PFOS have accepted all of the DWQI conclusions mentioned above, as well as other conclusions (e.g., importance of considering higher exposures to breastfed infants) from DWQI (2017, 2018).

Post, Gleason, Cooper (2017)

An invited review entitled *"Key scientific issues in developing drinking water guidelines for perfluoroalkyl acids: Contaminants of emerging concern"* whose authors include three current members of the Health Effects Subcommittee (K. Cooper, J. Gleason, G. Post) was published in the peer-reviewed journal PLOS Biology in 2017.

This publication discusses the conclusions about human health effects within the general population exposure range mentioned above and states that: "A distinctive feature of the dose-response curves for several effects (e.g., increased serum lipids and liver enzymes) is that they are steepest at low exposures, including those prevalent in the general population, with a much flatter slope approaching a plateau at higher exposures."

It is also stated that "human studies are preferred as the basis for drinking water guidelines when suitable data are available," while noting that limitations in the available human data had precluded their use as the primary basis of drinking water guidelines and that "this approach should be reconsidered if future studies provide further support for use of human data."

While noting the limitations of the available human data as the primary basis of drinking water guidelines, Post, Gleason, Cooper (2017) stated that: "… considerable evidence linking some PFAAs [perfluoroalkyl acids] with multiple human health effects even within the general population exposure range indicates the need for caution about additional exposure from drinking water." It further stated that "ongoing exposure to even relatively low drinking water concentrations of long-chain PFAAs substantially increases human body burdens, which remain elevated for many years after exposure ends," and that serum levels predicted from exposure to the USEPA (2016a,b) PFOA and PFOS Health Advisories of 70 ng/L exceed those associated with several health effects, indicating "that increases [in serum PFOA/PFOS levels] of this magnitude are not desirable and may not be protective of public health." Additionally, the higher exposures of infants, particularly those that are breastfed, was emphasized. It was noted that Minnesota Department of Health had developed a model (which was not yet published at the time) that considers the exposure to breastfed infants from PFAS in maternal drinking water and that this model was used to develop Minnesota's drinking water guidelines for PFOA and PFOS.

Post (2022)

Post (2022) is an invited perspective in the peer-reviewed journal Environmental Health Perspectives entitled "*Current Breast Milk PFAS Levels in the United States and Canada Indicate Need for Additional Monitoring and Actions to Reduce Maternal Exposures."* The author (G. Post) is a member of the Health Effects Subcommittee.

This publication reviews empirical data and modeling predictions demonstrating that exposures to PFAS (including PFOA and PFOS) in breastfed infants are much higher than in older individuals, both within the general population and when drinking water is contaminated. It also reviews recent epidemiological data (e.g., Abraham et al., 2020) indicating that infants' exposure to PFOA and PFOS through breast milk is associated with adverse health effects (e.g., decreased vaccine response).

APPENDIX 2: USE OF HUMAN DATA IN PFOA AND PFOS EVALUATIONS BY OTHER AUTHORITATIVE AGENCIES

Until recently, all toxicity factors and drinking water guidelines developed by federal, state, and international agencies for PFOA and PFOS were based on animal toxicology data. In addition to USEPA (2021a,b; 2022a,b), recent evaluations from several other authoritative groups including the European Food Safety Authority (EFSA, 2020), California EPA (CalEPA, 2021), and National Academy of Sciences and Medicine (NASEM, 2022) have also concluded that human epidemiological data for associations of health effects with PFOA and PFOS are appropriate as the basis for toxicity factors, drinking water guidelines, and/or other public health advice related to exposure to these and other PFAS. This appendix present summaries of the EFSA (2020), CalEPA (2021), and NASEM (2022) evaluations. In general, the conclusions and the numerical values developed by these authoritative groups provide additional support for health-based drinking water levels below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

European Food Safety Authority (EFSA) Tolerable Weekly/Daily Intakes for PFOA and PFOS (2020)

EFSA (2020) developed a Tolerable Daily Intake (TDI; similar to a Reference Dose) of 0.63 ng/kg/day for the total of PFOA, PFOS, perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS). As described below, this TDI is based on human epidemiological data for the association of PFAS and decreased vaccine response.

EFSA (2020) concluded that there is evidence for associations of PFOA, PFOS, and/or other long-chain PFAS with several non-cancer effects, including increased serum ALT, increased serum cholesterol, small decreases in birth weight, and decreased antibody response to vaccination, and that evidence for causality was strongest for effects on birthweight and decreased response to vaccination. EFSA (2020) further concluded that there is insufficient evidence for carcinogenicity of PFOA and PFOS in humans. It is noted that this conclusion was made prior to the publication of Shearer et al. (2021), which reports association of PFOA with increased risk of kidney cancer in the general population.

Consistent with DWQI (2017a), EFSA (2020) identified delayed mammary gland development in mice as the most sensitive developmental effect of PFOA and noted that this effect had not been evaluated for other PFAS. EFSA identified a serum PFOA LOAEC of "around 20 ng/L" in offspring corresponding to a maternal LOAEC of 66 ng/L, with no NOAEC identified. These conclusions are consistent with the DWQI (2017a) serum PFOA BMDL of 22.9 ng/ml for delayed mammary gland development in offspring on postnatal day 21.

EFSA (2020) selected decreased vaccine response as the critical effect for quantitative risk assessment and noted that this effect is consistent with decreased immune system response in laboratory animal studies of PFOA and PFOS. Relevant to selection of this endpoint, EFSA (2020) also concluded that there is some evidence for association of PFAS with infectious disease, but that there is a need for more studies with "objective measures of infection (not self-

reports)," are needed. EFSA (2020) also noted that delayed mammary gland development in mice occurs at similar serum PFOA levels as decreased vaccine response in humans, but that this effect has not been studied for other PFAS or in humans.

EFSA (2020) based its quantitative evaluation on the total concentration of PFOA, PFOS, perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS). These four long-chain PFAS are bioaccumulative, with human half-lives of several years, and they are the PFAS that are most commonly detected in human blood serum. EFSA further used the "pragmatic" assumption that the four PFAS are equally potent in causing the immune system effect (i.e., decreased vaccine response) being evaluated.

Specifically, EFSA (2020) evaluated two studies of decreased vaccine response and PFAS, Grandjean et al. (2012) and Abraham et al. (2020). EFSA (2020) identified a NOAEC of 27.0 ng/ml for the total serum concentration of PFOA, PFOS, PFNA, and PFHxS at age 5 years and decreased diphtheria vaccine response at age 7 years in Grandjean et al. (2012). EFSA (2020) performed BMD modeling on these data but the BMDL was "not considered suitable for risk assessment" due to the large BMD/BMDL ratio. For Abraham et al. (2020), EFSA identified a $BMDL_{10}$ of 17.5 ng/ml for the total serum concentration of PFOA, PFOS, PFNA, and PFHxS and decreased response to the diphtheria vaccine in 1 year old children who had been predominantly breastfed. Toxicokinetic modeling was used to develop a maternal dose of 0.63 ng/kg/day (identified as the TDI for the total of the four PFAS) that is predicted to result in a serum level of 17.5 ng/ml (the $BMDL_{10}$) in 1 year old children after 12 months of breastfeeding.

When comparing the EFSA (2020) TDI of 0.63 ng/kg/day to the USEPA (2021a,b) RfDs, it should be noted that no uncertainty factors were applied to the POD (i.e., BMDL) in development of the EFSA (2020) TDI of 0.63 ng/kg/day for the total of four long-chain PFAS. In contrast, the USEPA RfDs of 0.0015 ng/kg/day for PFOA and 0.0079 ng/kg/day for PFOS include an uncertainty factor of 10 for intra-individual variability.

The EFSA (2020) TDI of 0.63 ng/kg/day is based on PFAS exposure and serum levels in lactating women. Because serum levels of long-chain PFAS result from exposures over at least several years, the drinking water ingestion rate for women of childbearing age (rather than the higher rate for lactating women) is more appropriate for use in development of health-based drinking water guideline from this TDI. The 90^{th} percentile drinking water ingestion rate (direct and indirect consumption of community water, consumers only) for women of childbearing age (13 to <50 years) from the 2019 update of the *USEPA Exposure Factors Handbook chapter on Ingestion of Water and Other Select Liquids* (Table 3-63) (USEPA, 2019) is 0.0354 L/kg/day. The health-based drinking water level based on this ingestion rate and the default Relative Source Contribution factor of 20% is 3.6 ng/L, which is below the New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS. Additionally, it should be noted that this TDI applies to total exposure of PFOA, PFOS, PFNA, and PFHxS, and drinking water levels that consider toxicological interactions of multiple PFAS would be lower than those that do not consider such interactions, such as the current NJ Health-based MCLs.

Draft California EPA (2021) evaluations of PFOA and PFOS (2021)

California EPA (2021) developed toxicity factors (Acceptable Daily Doses [ADDs] for non-cancer effects similar to RfDs; CSFs) and health-based drinking water levels for PFOA and PFOS that consider carcinogenic and non-carcinogenic effects. The draft California EPA (2021) drinking water Public Health Goals (PHGs) of 0.007 ng/L for PFOA and 1 ng/L for PFOS are based on CSFs and the 1 in 1 million (1×10^{-6}) risk level, which is also used for New Jersey Health-based MCLs. California EPA (2021) also developed drinking water Health Protective Concentrations (HPCs) of 3 ng/L for PFOA and ng/L for PFOS based on ADDs (analogous to RfDs) for non-cancer effects that are less stringent than the PHGs. The draft California EPA (2021) document provides a thorough review of the relevant scientific information. The draft document underwent external peer review, and the peer review report (California EPA, 2022) indicates that the peer reviewers generally agreed with the California EPA (2021) conclusions.

California EPA (2021) concluded that adverse human health effects occur from exposure to PFOA and PFOS at "environmental levels," and that "effects seen in humans are supported by studies in laboratory animals…" California EPA (2021) further concluded that there is epidemiological evidence for associations of both PFOA and PFOS with immune system toxicity and increased total cholesterol, as wells as suggestive epidemiological evidence for association with pre-eclampsia and pregnancy-related hypertension. Additionally, for PFOA, California EPA (2021) concluded that there is epidemiological evidence for increased risk of both kidney cancer and liver toxicity.

Public Health Goals (PHGs) based on cancer risk

California EPA (2021) stated that "based on the evidence of cancer in human and animal studies.., …PFOA and PFOS should be evaluated as carcinogens."

For PFOA, California EPA (2021) developed a CSF of 0.0026 $(ng/kg/day)^{-1}$ (2600 $[mg/kg/day]^{-1}$] based on human epidemiological data for increased risk of kidney cancer from two studies, Shearer et al. (2021) and Vieira et al. (2013). California EPA (2021) concludes that both of these studies "meet most, if not all, of the criteria commonly used to evaluate causal inference (Hill, 1965)" and provides a detailed basis for development of the CSF. The CSF is based on the geometric mean of the CSFs of 0.00637 $(ng/kg/day)^{-1}$ from Shearer et al. (2021), which is a study of the general population, and 0.00105 $(ng/kg/day)^{-1}$ from Vieira et al. (2013), which is a study of the C8 Health Study population with elevated exposure to PFOA from drinking water. These CSFs in terms of external dose $(ng/kg/day)^{-1}$ were developed from CSFs in terms of serum PFOA level of 0.00178 $(ng/ml)^{-1}$ from Shearer et al. (2021) and 0.00029 $(ng/ml)^{-1}$ from Vieira et al. (2013) using a clearance factor of 0.28 ml/kg/day developed by California EPA. It is noted the serum level CSFs from Shearer et al. (2021) developed by California EPA (2021) and USEPA (2021a) are identical. Steenland et al. (2022) also developed a CSF from Shearer et al. (2021) and Vieira et al. (2013) using a different modeling approach and came to similar conclusions as California EPA (2021) and USEPA (2021a). This is discussed further in the section on "*Additional Discussion of Key Health Endpoints Including Key Studies Not Included in DWQI PFOA (2017a) and PFOS (2018) Evaluations*" below.

The California EPA (2021) PHG for PFOA of 0.007 ng/L is based on the CSF of 0.0026 $(ng/kg/day)^{-1}$, a cancer risk level of 1 in 1 million (1×10^{-6}), and a drinking water ingestion rate of 0.053 L/kg/day (California's default ingestion rate, which is the 95th percentile age-weighted value for age 0 – 70 years). Using the New Jersey default drinking water exposure assumptions (80 kg body weight and 2.4 L/day water ingestion; DWQI, 2021) and the 1 in 1 million risk level also used by New Jersey, the health-based drinking water concentration based on this CSF would be 0.012 ng/L, far below the New Jersey PQL of 6 ng/L.

California EPA (2021) concluded that human data for PFOS does not support CSF development. The CSF for PFOS is based on tumor incidence from a chronic rat study (Butenhoff et al., 2012). CSFs were developed for liver tumors, pancreatic tumors, and combined liver and pancreatic tumors in males, and for liver tumors in females. The most stringent CSF of 15.6 $(mg/kg/day)^{-1}$ for combined liver and pancreatic tumors in male rats was selected. The CSF of 15.6 $(mg/kg/day)^{-1}$, a cancer risk level of 1 in 1 million (1×10^{-6}), and the lifetime drinking water ingestion rate of 0.053 L/kg/day were used to derive a PHG of 1 ng/L. It is noted that the DWQI (2018) developed a CSF of 9 $(mg/kg/day)^{-1}$ for liver tumors in female rats from Butenhoff et al. (2012) but concluded that this CSF is uncertain and should only be used for range-finding purposes.

Health Protective Concentrations (HPCs) based on non-cancer effects

For non-cancer effects of PFOA in humans, California EPA (2021) identified PODs for multiple studies and endpoints in terms of serum PFOA concentration ranging from 2.8 to 19.9 ng/ml. Studies and endpoints evaluated included decreased antibody response to multiple vaccines (Abraham et al., 2020; Grandjean et al., 2017), increased in serum levels of the liver enzyme ALT, and/or increased risk of clinically defined high elevated ALT (Darrow et al., 2016; Gallo et al., 2012), and increased serum cholesterol and/or increased risk of clinically defined high cholesterol from (Lin et al., 2019; Dong et al., 2019; Steenland et al., 2009). A No Observed Adverse Effect Concentration (NOAEC), Lowest Adverse Effect Concentration (LOAEC) and/or BMDL was identified for each endpoint. In some cases, multiple NOAECs or BMDLs using different dose-response analyses were developed for the same study and endpoint.

Similarly, for non-cancer effects of PFOS in humans, California EPA (2021) identified PODs for several studies and endpoints in terms of serum PFOS concentration ranging from 12.3 to 24.1 ng/ml. Studies and endpoints evaluated included decreased antibody response to tetanus and diphtheria vaccines (Budtz-Jorgensen and Grandjean, 2018) and increased serum cholesterol and/or increased risk of clinically defined high cholesterol from Dong et al. (2019), Steenland et al. (2009), Frisbee et al. (2010), and Starling et al. (2014). The PODs included NOAECs, LOAECs, and/or BMDLs for each endpoint.

It is noted that California EPA (2021) identified NOAECs of 4.75 ng/ml for PFOA and 20.6 ng/ml for PFOS for decreased response to diphtheria vaccine in Grandjean et al. (2012) from categorical data presented in EFSA (2020) that were not included in the Grandjean et al. (2012) publication. However, California EPA (2021) did not support use of the much lower $BMDL_{05}$

values developed by Budtz-Jorgensen and Grandjean (2018) from the Grandjean et al. (2012) data (0.20 and 0.17 ng/ml for decreased response to diphtheria and tetanus vaccines, respectively, for PFOA; 0.54 and 0.72 for decreased response to diphtheria and tetanus vaccines, respectively, for PFOS), or the similar $BMDLs_{05}$ for these data developed by California EPA (2021). California EPA (2021) stated that these BMDLs were not selected as the basis for ADDs (analogous to RfDs) because they were well below the observed range of serum values and had large BMD:BMDL ratios, and that "the most likely reason the BMD:BMDL ratios were so large was the high degree of variability (i.e., the very large standard deviations) in antibody levels seen in each [PFOA and PFOS] exposure category." These California EPA conclusions are notable because USEPA (2021a) selected the $BMDLs_{05}$ of 0.17 ng/ml for decreased response to tetanus vaccine for PFOA and 0.54 ng/ml for decreased response to diphtheria vaccine for PFOS from Budtz-Jorgensen and Grandjean (2018) as the PODs for its draft RfDs.

California EPA (2021) also developed PODs for PFOA and PFOS from animal data. For PFOA, PODs for hepatic effects were developed from four different mouse studies; these effects were identified as the most sensitive effects of PFOA in laboratory animals. For PFOS, PODs were developed for hepatic effects from two mouse studies and one rat study, for immunotoxicity in two mouse studies, and for thyroid toxicity in one rat study; these were identified as the most sensitive effects of PFOS in laboratory animals. However, California EPA (2021) did not pursue development of ADDs (analogous to RfDs) from these PODs because they concluded that there were sufficient human data to develop ADDs without the uncertainty of interspecies extrapolation.

The PODs selected as the basis for the draft California EPA (2021) ADDs are the NOAEC of 9.8 ng/ml for increased risk of clinically defined elevated serum ALT from Gallo et al. (2012) for PFOA and the LOAEC of 16.4 ng/ml for increased risk of clinically defined high serum cholesterol from Steenland et al. (2009) for PFOS. The rationale for the choice of these PODs included very large size of the studies, clinical relevance of the endpoints, consistency of associations with these endpoints in multiple studies using multiple approaches for analysis, and several other considerations discussed in detail in California EPA (2021).

The ADD of 0.87 ng/kg/day for PFOA was derived by applying a clearance factor of 0.28 ml/kg/day to the POD of 9.8 ng/ml to convert it to an external dose (ng/kg/day) and application of an uncertainty factor of $\sqrt{10}$ (approximately 3) for intraspecies variability and potentially more sensitive immune system effects. The ADD of 0.64 ng/kg/day for PFOS was derived by applying a clearance factor of 0.39 ml/kg/day to the POD of 16.4 ng/ml to convert it to an external dose and application of a total uncertainty factor of 10 ($\sqrt{10}$ for extrapolation from LOAEC to NOAEC and $\sqrt{10}$ for intraspecies variability). It is noted that these clearance factors were derived by California EPA (2021) and are higher than the USEPA (2016a,b) and USEPA (2021a,b) clearance factors. All other things being equal, the use of the higher California (2021) clearance factors results in higher ADDs than if the USEPA clearance factors had been used.

HPCs (health-based drinking water values for non-cancer effects) of 3 ng/L for PFOA and 2 ng/L were developed using California's default drinking water ingestion rate of 0.053 L/kg/day (described above) and the default Relative Source Contribution factor of 20%.

The health-based drinking water levels using the California ADDs for non-cancer effects and the New Jersey default exposure assumptions of 80 kg body weight and 2.4 L/day water ingestion (DWQI, 2021) are 5.8 ng/L for PFOA and 4.3 ng/L for PFOS, which are essentially identical to the NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

National Academy of Sciences, Engineering and Medicine (NASEM, 2022) report: "Guidance on PFAS exposure, testing, and clinical follow-up"

At the request of the Agencies for Toxic Substances and Disease Registry (ATSDR) and the National Institute of Environmental Health Sciences (NIEHS), NASEM formed an *ad hoc* committee that developed a report (NASEM, 2022) providing recommendations to clinicians on testing for PFAS and clinical care for patients with PFAS exposure. Some of the NASEM (2022) conclusions are relevant to the current Health Effects Subcommittee evaluation. Specifically, NASEM reviewed the scientific literature on health effects of PFAS in humans, identified serum PFAS concentrations at which the risk of health effects may be increased, and recommended actions to reduce exposure including home drinking water filters when PFAS in drinking water is elevated.

NASEM (2022) reviewed existing conclusions about PFAS and health effects from authoritative bodies including the C8 Science Panel (2012), European Food Safety Authority (EFSA, 2020), Organisation for Economic Co-operation and Development (OECD, 2013), International Agency for Research on Cancer (IARC, 2016), USEPA (2016a, b), National Toxicology Program (NTP, 2016), and ATSDR (2021). NASEM (2022) stated that the ATSDR (2021) evaluation was given the most emphasis because it included the most recent literature search (through 2018) and evaluated the largest number of PFAS. Additionally, systematic reviews meeting certain criteria that were identified in a June 28, 2021 literature search performed by NASEM and published after 2018 were used as secondary sources of information. Finally, human studies of health effects of PFAS identified in a March 30, 2021 search of the primary scientific literature performed by NASEM were considered if they met certain criteria (published after 2018; not included in ATSDR, 2021; not cross-sectional). NASEM (2022) stated that most of the studies that they reviewed were "not conducted among people known to have high exposures to PFAS" (e.g., were general population studies). It should be noted that several key publications discussed in this memorandum (see section on "*Additional Discussion of Key Health Endpoints Including Key Studies Not Included In DWQI PFOA (2017a) and PFOS (2018) Evaluations"*, below) were published after the dates of the NASEM literature searches and were thus not considered by NASEM (2022).

Based on the review process described above, NASEM (2022) concluded that there is "sufficient evidence" of an association with PFAS for decreased antibody response to vaccination or infection in adults and children, dyslipidemia (e.g., increased serum cholesterol) in adults and

children, decreased infant and fetal growth, and increased risk of kidney cancer in adults. "Sufficient evidence" was defined by NASEM (2022) as "based on strong evidence, there is high confidence that there is an association between exposure to PFAS and the health outcome. It is unlikely that the association is due to chance or bias."

Additionally, NASEM (2022) concluded that there is "limited or suggestive evidence" of an association with PFAS for increased risk of breast cancer in adults, liver enzyme alterations (in adults and children), increased risk of pregnancy-induced hypertension (gestational hypertension and preeclampsia), increased risk of testicular cancer in adults, thyroid disease and dysfunction in adults, and increased risk of ulcerative colitis in adults. "Limited or suggestive evidence" was defined as "based on limited evidence, there is moderate confidence that there is an association between exposure to PFAS and the health outcome. It is possible that the association is due to chance or bias."

NASEM (2022) stated that these conclusions apply to all seven PFAS currently reported in the National Health and Nutrition Examination Survey (NHANES), which are PFOA, PFOS, PFNA, PFHxS, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and methyl perfluorooctane sulfonamidoacetic acid (MeFOSAA) (CDC, 2022), while recognizing that differences exist among these PFAS. Specifically, NASEM (2022) stated: "Most people are exposed to mixtures of PFAS such that specific effects are difficult to disentangle. Considering these issues, and recognizing that some PFAS are infrequently measured, the committee provided one strength-of-evidence determination for all PFAS for each health effect, recognizing that providing one conclusion across PFAS may not account for the distinct physical, chemical, and toxicological properties of each type of PFAS."

NASEM (2022) recognized drinking water as an important source of PFAS exposure and recommended that: "Clinicians should advise patients with elevated PFAS in their drinking water that they can filter their water to reduce their exposure. …Individuals who cannot filter their water can use another source of water for drinking."

NASEM (2022) further recommended that clinicians should "offer PFAS [blood] testing to patients likely to have a history of elevated exposure" including those with potential occupational exposure and those who have lived in communities known to have PFAS contamination or "where PFAS contamination may have occurred, such as near facilities that use or have used fluorochemicals, commercial airports, military bases, wastewater treatment plants, farms where sewage sludge [biosolids] may have been used, or landfills or incinerators that have received PFAS-containing waste."

Of particular relevance to the current Health Effects Subcommittee evaluation, NASEM (2022) identified serum/plasma PFAS concentrations of potential concern, based on the total concentration of PFOA, PFOS, and the five other PFAS currently reported in NHANES (listed above). NASEM (2022) concluded that adverse health effects are "not expected" at serum concentrations of < 2 ng/ml for the total of the seven PFAS; that there is "a potential for adverse effects, especially in sensitive populations" at serum concentrations of 2 – 20 ng/L for the total

of the seven PFAS; and that there is an "increased risk of adverse effects" at serum concentrations of > 20 ng/ml for the total of the seven PFAS. They further stated that "there may not even be a level of PFAS exposure without some biological effect."

The serum PFAS levels (2 ng/L; 20 ng/L) identified by NASEM (2022) are based on human biomonitoring (HBM) values developed by the German HBM Commission (Hölzer et al., 2021). Two levels of HBM values were developed. HBM-I values are levels for which "there is no reliable evidence for a health risk…, but … there is no sufficient evidence for safety in terms of health," at which "increased precautionary measures" such as exposure reduction or elimination should be taken, and HBM-II values are levels which may lead to adverse health effects when exceeded (Hölzer et al., 2021; Schümann et al., 2021).

For HBM-I values, the German HBM Commission concluded that there was evidence for associations of serum/plasma PFOA- and PFOS levels and "fertility and pregnancy, weights of newborns at birth, lipid metabolism, immunity, sex hormones and age at puberty/menarche, thyroid hormones, onset of menopause [and] metabolism, and that there were "significant contrasts" for these effects at within blood plasma concentrations ranges of 1-10 ng/ml for PFOA and 1–15 ng/ml for PFOS. The HBM-I values were established as 2 ng/ml for PFOA and 5 ng/ml for PFOS in 2016 (Hölzer et al., 2021).

For HBM-II values, the evaluation focused on the following endpoints: decreased birth weight/developmental toxicity, decreased fertility, decreased antibody formation, increased cholesterol concentrations (LDL and total), and Type II diabetes. It was concluded that PODs for quantitatively defined changes relevant to deriving HBM-II values were in the range of 3-10 ng/L for PFOA and 1–30 ng/ml for PFOS. HBM-II values of 10 ng/ml for PFOA and 20 ng/ml for PFOS, with lower values of 5 ng/ml for PFOA and 10 ng/ml for PFOS for women of child-bearing age, were established in 2019 (Schümann et al., 2021).

As mentioned above, NASEM (2022) concluded that there is "a potential for adverse effects, especially in sensitive populations," at serum concentrations of 2 – 20 ng/L for the total of the seven PFAS, "increased risk of adverse effects" at total serum concentrations of > 20 ng/ml, and that "there may not even be a level of PFAS exposure without some biological effect." For these reasons, NASEM (2022) recommended reduction of PFAS exposure if source(s) are known when total serum PFAS concentrations are >2 ng/ml and recommended use of home water filters when PFAS is elevated in drinking water. NASEM (2022) also recommended clinical monitoring beyond the usual standard of care (lipid screening beginning at a younger age and more frequently; regular screening for thyroid function, testicular cancer, kidney cancer, and ulcerative colitis) when serum concentrations are >20 ng/L.

Based on NHANES data, NASEM (2022) estimated that the total serum concentration of the seven PFAS is >2 ng/ml in 98% of the U.S. population, with 2-20 ng/L in 89% and >20 ng/ml in 9%. Relevant to the current Health Effects Subcommittee evaluation, it is important to note that serum levels of just the two PFAS addressed in the current Health Effects Subcommittee evaluation exceed 2 ng/ml in a considerable portion of the U.S. population, including those

whose drinking water is not known to be contaminated. The geometric mean and median serum concentrations from the most recent NHANES (2017-18) are 1.42 and 1.47 ng/ml, respectively, for PFOA and 4.25 and 4.3 ng/L, respectively, for PFOS. NHANES (2017-18) serum levels of the other five PFAS included by NASEM (2022) are much lower; the geometric mean and median for PFHxS are 1.08 and 1.10 ng/L, respectively, and for the other four PFAS, the ranges of geometric means and medians range are 0.0125-0.411 and 0.100-0.400 ng/L, respectively.

In summary, NASEM (2022) concluded that there is a potential risk of adverse effects at serum PFAS levels found in a large percentage of the general population (with PFOA and PFOS the major contributors), including in many individuals with no or minimal exposure through drinking water. This conclusion supports the need to minimize exposure to PFOA and PFOS in drinking water to the greatest extent that is feasible. As such, the NASEM (2022) conclusion supports the development of Health-based MCLs below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

APPENDIX 3: REVIEW OF RECENT INFORMATION ON KEY HEALTH ENDPOINTS

Numerous peer-reviewed publications about PFOA, PFOS, and PFAS in general have become available since the Health Effects Subcommittee completed its evaluations of PFOA (DWQI, 2017a) and PFOS (DWQI, 2018). These include many additional studies reporting associations of health effects with PFOA and PFOS within the general population exposure range, some of which were included in the draft USEPA (2021a,b) PFOA and PFOS evaluations and others that were not. Additionally, recent laboratory animal studies demonstrate concordance with some of the health effects reported in humans. Overall, these newer data provide further support for the use of human data in risk assessment of PFOA and PFOS.

This appendix provides the Subcommittee's review of additional information for the four non-cancer endpoints with the most consistent epidemiological evidence for associations with PFOA and PFOA. For each of these four endpoints (decreased antibody response to vaccination, hepatic effects – increased serum ALT, decreased birth weight, increased serum lipids – cholesterol), the evaluations performed by USEPA (2016a,b), DWQI (2017a, 2018), and USEPA (2021a,b), as well as relevant USEPA SAB (2022) comments, are summarized. Additional key studies not included in these evaluations are also discussed when appropriate. The section also reviews recent epidemiological evidence for cancer and PFOA, as well as a recent study of overall mortality and PFAS including PFOA and PFOS. Finally, the epidemiological evidence for impacts of PFAS on duration of breast feeding is reviewed since this is an important effect that has been consistently reported in multiple studies.

It is important to emphasize that the Subcommittee did not conduct a comprehensive review of all studies that have become available since the DWQI (2017a, 2018) completed its evaluations of PFOA and PFOS. A review of all of the numerous newer studies would be a massive undertaking that is beyond the scope of this Health Effects Subcommittee task.

Non-cancer effects

Antibody response to vaccination

USEPA (2016a,b) reviewed three human studies of antibody response to vaccinations and PFOA and PFOS (two in children, each from a different location; one in adults). It concluded that there are associations of PFAS, especially PFOA, with decreased immune response in children including within the general population exposure range. However, for reasons discussed above, USEPA (2016a,b) did not use human data in general as the basis for RfD development.

DWQI (2017a, 2018) reviewed five studies (two in children, each from a different location; one in adolescents; one in adults) of antibody response to vaccinations. These five studies included three studies reviewed by USEPA (2016a,b) and two additional studies.

For PFOA, DWQI (2017a) concluded that the "…review of epidemiologic studies provides evidence of consistent findings among studies of decreased antibody concentrations following vaccination and PFOA. There is epidemiologic evidence of temporality. However, there are a

limited number of comparisons across the same vaccination types, making consistency/specificity difficult to evaluate."

Similarly, for PFOS, DWQI (2018) concluded that: "The total number of epidemiology studies examining antibody response to vaccines is relatively small (n = 5), and not all vaccine types were evaluated in each study. Nonetheless, the study findings are consistent and support a potential for PFOS to reduce vaccine response, particularly for some vaccine types in children. The effects of PFOS on suppression of vaccine response appears to occur at or close to levels of PFOS exposure prevalent in the general population. However, there is not sufficient information to evaluate associations of PFOS and vaccine response in adults." A peer-reviewed publication on immune system effects of PFOS by scientists from the NJDEP Division of Science and Research, including a member of the Health Effects Subcommittee (Pachkowski, Post, Stern, 2019), reviewed the same five studies and another more recent study and concluded that there is evidence that PFOS is "associated with a decrease in some vaccine antibody responses following vaccination."

DWQI (2017a, 2018) also concluded that PFOA and PFOS cause immune system suppression in laboratory animals, specifically mice. The DWQI (2018) identified decreased antibody response to a foreign antigen (sheep red blood cells) in mice (analogous to decreased antibody response to vaccines in humans) as the most sensitive toxicological effect of PFOS. An RfD for this effect is the basis of the DWQI (2018) Health-based MCL for PFOS.

Additionally, DWQI (2017a, 2018) noted that the National Toxicology Program (NTP, 2016) conducted a systematic review of immunotoxicity of PFOA and PFOS, including human and animal studies and mechanistic data. The NTP (2016) review concluded that PFOA and PFOA are "presumed to be … immune hazard[s] to humans based on a high level of evidence that …[they] suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans."

USEPA (2021a,b) reviewed six recent general population studies from several locations (five in children, one in adolescents) of PFOA and PFOS and antibody response to vaccination that were not considered by DWQI (2017a, 2018). These studies included Abraham et al. (2020), the study of vaccine response and serum PFAS levels in one year old German children that was used as the basis for the EFSA (2020) Tolerable Daily Intake for the total of PFOA, PFOS, PFNA, and PFHxS.

For PFOA, USEPA (2021a) concluded that: "The findings from human epidemiological studies are generally consistent with an association between PFOA exposure and immunosuppression in children. Evidence in adults does not indicate an association with immunosuppression, but high-quality studies are not available." USEPA (2021b) similarly concluded for PFOS that: "Results from human epidemiological studies are most consistent for antibody response to vaccination in children, and multiple medium confidence studies report a positive association for this outcome."

USEPA (2021a,b) also reviewed two additional studies of serum PFOA and PFOS and antibody levels in Chinese populations. Zeng et al. (2019) reported associations of serum PFOA and PFOS in cord blood (i.e., at birth) with decreased levels of two viruses that cause hand, foot and mouth disease (enterovirus 71 and coxsackievirus A 16) at age 3 months, including increased risk of antibodies below clinically protective levels. Zeng et al. (2020) reported associations of serum PFOA and PFOS with decreased levels of hepatitis B surface antibody in adults. USEPA (2021a,b) stated that the results of these studies are consistent with associations with decreased antibody response to vaccination, while noting the limitations of these studies.

Additionally, USEPA SAB (2022) identified two studies of PFAS exposure and reduced vaccine response (Shih et al., 2021; Timmermann et al., 2022a) that were not considered by USEPA (2021a, b).

Shih et al. (2021) evaluated associations of PFAS and antibody response to vaccines in a Faroese cohort that was followed from birth until age 28 years. Associations of antibody response to four vaccines (hepatitis type A and hepatitis type B, n=399; diphtheria and tetanus, n=281) six months after they were administered at age 28 years and serum PFOA, PFOS, PFHxS, PFNA, and PFDA at multiple timepoints (cord blood at birth, and ages 7, 14, 22, and 28 years) were evaluated. There were trends for associations of PFOA at age 14 years and decreased hepatitis type A antibody at age 28 years, and PFOA at ages 22 and 28 years and decreased hepatitis type B antibody at age 28 years, but these trends were not statistically significant. There were also sex-specific associations (some inverse, some positive) for antibodies to hepatitis type A vaccine at age 28 years and PFAS at birth (cord blood) and at ages 7 and 14. No inverse associations of PFAS and response to diphtheria or tetanus vaccines at age 28 years were observed. The authors concluded that: "Future studies are needed to confirm these findings and further investigate the effects of PFASs on adult immune function."

Timmermann et al. (2022a) evaluated associations of serum PFAS (PFOA, PFOS, PFHxS, PFNA, PFDA, PFUnDA [perfluoroundecanoic acid; C11], PFHpS [perfluoroheptane sulfonate]) and antibody response to tetanus and diphtheria vaccines in children age 7-12 years from Greenland. The total study population included 338 children, of whom 175 had a known vaccination date. A high percentage of subjects had antibodies below the protective threshold (12% for tetanus vaccine and 52% for diphtheria vaccine in the whole study group; 3% for tetanus vaccine and 41% for diphtheria vaccine in the subset with known vaccination date). Statistically significant associations in antibody response to the diphtheria vaccine and PFOS and PFHxS were observed in the subset of subjects with known vaccination date, after adjustment for duration of breastfeeding and area of residence. Additionally, the odds ratio for being below the protective threshold for diphtheria vaccine antibodies in the subset with vaccine date records and the adjustments mentioned above was increased for all seven PFAS evaluated, but the increase was not statistically significant for PFOA, PFUnDA, and PFHpS. In the subset of subjects (n=57) with vaccine date records and date for maternal serum PFAS during pregnancy, there were no consistent associations of maternal serum PFAS and vaccine response in offspring.

USEPA SAB (2022) agreed with USEPA (2021a,b) that human data for associations of PFOA and PFOS with decreased vaccine response in children are appropriate as the basis for RfD development. They discussed that this effect is an indication of an impact on immune system function and that it is "an adverse immunological outcome." USEPA SAB (2022) further concluded that: 1) decreased response to vaccination is associated with PFOA and PFOS in epidemiological studies "of different study populations across a range of vaccine types;" 2) at least two studies reported associations of PFOA and/or PFOS with antibody response to vaccines below the clinically defined protective threshold; and 3) the human data are consistent with laboratory animals studies showing that PFOA and PFOS suppress the antigen-specific antibody response (analogous to vaccination in humans).

The Health Effects Subcommittee has identified two additional relevant studies (Pennings et al., 2016; Porter et al., 2022) that were not considered by DWQI (2017a, 2018), USEPA (2021a,b) or USEPA SAB (2022).

Pennings et al. (2016) examined associations of gene expression in umbilical cord blood (i.e., neonatal blood) from up to 3 days after delivery (n=66) with 1) maternal serum PFAS (PFOA, PFOS, PFNA, PFHxS) levels; 2) response to rubella vaccine at age 3 years (n=58), and 3) the number of common cold episodes until age 3 years (n=73). The study group was part of an established Norwegian cohort of pregnant mothers and their children. Maternal serum PFAS (defined as two or more of the four PFAS evaluated), rubella antibody levels, and episodes of common cold were associated with changed expression of 578, 580, and 1231 genes, respectively. Expression of 27 genes was associated with both PFAS and common cold, and expression of 26 genes was associated with both PFAS and rubella antibody levels, and one gene (cytokine-like 1; CYTL1) was common to both of these gene sets. Both gene sets "showed enrichment for similar functions (including immunology and development)." *In silico* analysis was performed to evaluate whether common mechanisms are associated with PFOA exposure, response to rubella vaccine, and common cold episodes. Genes that were correlated with both exposure to PFAS and rubella vaccine response, or both exposure to PFAS and common colds, were associated with processes including immune system, apoptosis, development, signal transduction, and transcription. The authors concluded that the gene expression changes that they observed are consistent with the two modes of action for immunotoxicity caused by PFAS that were previously proposed by Corsini et al. (2014) – pathways regulated by peroxisome proliferator activated receptors (PPARs) and pathways regulated by NF-κB.

A recent study by Porter et al. (2022) evaluated associations of antibody response to COVID-19 vaccines and serum PFAS (PFOA, PFOS, PFNA, PFHxS) in a study group composed of 3M employees and retirees (n=757 observations of vaccine response from 415 subjects). The subjects currently or previously work(ed) at a facility that manufactured PFAS, a facility where there was limited use of PFAS, and/or a facility where PFAS was not used. As such, PFAS exposures ranged from levels prevalent within the general population to highly elevated (50^{th} percentile, 95^{th} percentile, and maximum, respectively: for PFOA – 1.63, 31.7, and 139.0 ng/ml; for PFOS – 7.46, 121.4, and 432 ng/ml). Two indicators of antibody response to COVID-19 vaccine were evaluated, anti-spike IgG and neutralizing antibodies. Decreased levels of both of

these measures of antibody response were consistently correlated with each of the four PFAS in both an unadjusted model and in several adjusted models (see below). These associations were statistically significant for both measures of antibody response and PFOS, PFOS, and PFHxS in both the unadjusted analysis and with adjustment for age, gender, race, body mass index, smoking, immunocompromising conditions, corticosteroid use in past 30 days in the absence of immunocompromising conditions, and time since antigenic stimulus (COVID-19 diagnosis or vaccination). In models that further adjusted for antigenic stimulus group (i.e., COVID-19 infections; number of vaccines; type(s) of vaccine [Moderna, Pfizer, J&J]) or interaction between antigenic stimulus group and time since antigenic stimulus, associations remained consistently inverse but none of the associations were statistically significant (i.e., 95% confidence intervals included zero). The authors concluded that "… the fully adjusted coefficients relating concentration of vaccine-induced antibodies to COVID-19 and IQR difference in serum concentration of PFOS, PFOA, PFHxS, and PFNA were inverse but small with confidence intervals that included zero. Our analysis showed that the coefficient for the four PFAS examined in detail was considerably affected by adjustment for antigenic stimulus group." It is noted that the authors are employees of 3M and Ramboll, a consulting firm that was funded by 3M for its work on this project, and that publication includes the following statement: "The final version of this manuscript was negotiated between the employees of Ramboll and 3M."

Hepatic Effects – Alanine Aminotransferase (ALT)

For PFOA, USEPA (2016a) reviewed six occupational studies, two studies of communities with contaminated drinking water, and one general population study that evaluated associations of PFOA and markers of liver function. USEPA (2016a) concluded that serum PFOA was associated with increased serum levels of the liver enzyme ALT in all three types of populations.

For PFOS, USEPA (2016b) reviewed only two studies with general population level exposures. While both studies reported associations of serum PFOS with ALT, USEPA (2016b) concluded that the influence of other co-occurring PFAS could not be evaluated and that the evidence was not strong enough to support the conclusion that there is an association with PFOS.

DWQI (2017a) reviewed 18 studies that evaluated serum PFOA and ALT (10 occupational, three from communities with contaminated drinking water, 5 general population) and concluded that there was evidence to support a causal relationship between PFOA and increased serum ALT. Fewer studies were available for PFOS (two occupational and two with general population level exposures), and the DWQI (2018) concluded that these studies did not provide consistent results for associations of PFOS with ALT and other liver enzymes.

Regarding clinical relevance of increased ALT, the DWQI (2017a) further concluded that, although the increases in ALT (and other endpoints, such as decreased birth weight; see below) associated with PFOA were relatively small, such effects are "of public health concern because population-level changes of this magnitude will result in a shift in the overall distribution of values such that the number of individuals with clinically abnormal values is increased."

The USEPA SAB (2022) agreed with this DWQI conclusion, stating that: "In studies where the number of subjects with clinically abnormal values was not specifically evaluated, an increase in the number of subjects with a clinically abnormal value is also expected from the overall change (shift in the distribution curve) in the abnormal direction. While the clinical relevance of exposure to PFOA or PFAS cannot be predicted on an individual basis, the increased number of individuals within a population with clinically defined abnormal values is of public health concern."

Additionally, the DWQI (2017a) and publications by Health Effects Subcommittee members (e.g., Post, Gleason, Cooper, 2017) concluded that hepatic effects of PFOA and other PFAS in laboratory animals are concordant with results of human studies and provide further support for the consideration of these human effects for risk assessment. Hepatic toxicity is one of the most well-established toxicological effects of PFOA, PFOS, and other PFAS in laboratory animals. To the knowledge of the Health Effects Subcommittee, hepatic effects in laboratory animals have been reported for all PFAS that have been evaluated for such effects. The relevance of the hepatic effects of PFAS in rodents for human health risk assessment was previously subject to debate because of questions about the adversity of these hepatic effects and the human relevance of hepatic effects mediated by the nuclear receptor peroxisome proliferator-activated receptor-α (PPAR-α). The detailed evaluations of the hepatic effects and mode of action for PFOA and PFOS presented by the Health Effects Subcommittee (DWQI, 2017a; 2018) clearly show that the hepatic effects of PFOA and PFOS in rodents are adverse and relevant to humans. USEPA has now accepted the conclusion that hepatic effects of PFAS in rodents are sensitive, relevant, and adverse endpoints that are appropriate for use in human health risk assessment. For example, the recent final USEPA (2021d) Reference Dose for GenX is based on hepatic effects in mice, and hepatic effects in rodents are considered as potential critical endpoints in the draft USEPA (2021a,b) assessments of PFOA and PFOS and the draft USEPA IRIS assessments of perfluorohexanoic acid (USEPA, 2021f) and perfluorobutanoic acid (USEPA, 2021g).

USEPA (2021a) reviewed eight epidemiological studies of PFOA and ALT, including seven that were not available to DWQI (2017a), and USEPA (2021b) reviewed seven such studies for PFOS, including six that were not available to DWQI (2018). USEPA (2021a,b) concluded that there is consistent evidence for associations of both PFOA and PFOS and increased ALT. However, the draft USEPA (2021a,b) assessments did not consider increased ALT to be appropriate as the basis for RfD development, and USEPA (2021h) asked the USEPA SAB to provide its opinion on this question. As stated in the USEPA (2021h) charge questions to its SAB, USEPA did not consider increased ALT to be appropriate for RfD development because "the magnitude of the effect was not large compared to control levels; and concerns about the clinical relevance of the findings and non-specificity of the biomarkers relationship to adverse liver injury and disease" and asked the SAB if it agreed with this rationale.

In its responses to the USEPA (2021h) charge questions, the USEPA SAB (2022) stated that it disagreed with USEPA's rationale for dismissing associations of PFOA and PFOS with increased ALT as the basis for RfD development (discussed in detail below); the Health Effects Subcommittee agrees with these SAB conclusions. Additionally, the SAB noted that an

increased risk of clinically defined elevated ALT (i.e., not just a numerical increase within the normal range) is associated with PFOA and PFOS, as follows: "while most … studies did not evaluate the number of subjects with a clinically abnormal value for biomarkers, … Gallo et al. (2012) [for PFOA and PFOS] and Darrow et al. (2016) [for PFOA] reported clinically defined elevated ALT." The SAB also noted that the California EPA (2021) draft ADD (e.g., RfD) for PFOA is based on human data for increased risk of clinically elevated ALT and recommended that USEPA consider this California EPA approach.

To support its conclusions that epidemiological data for ALT and/or other hepatic effects of PFOA and PFOS are an appropriate endpoint for RfD development, the USEPA SAB (2022) noted that USEPA (2002) guidance for RfD development states that a RfD should be based on an adverse effect or a precursor to an adverse effect, and that increased ALT is indicative of liver damage. The SAB also noted that, while increased ALT is not a clinical disease, this is also true of other effects considered appropriate for RfD development that have similar levels of evidence as ALT, including decreased birth weight, increased serum lipids, and decreased antibody response to vaccinations. Additionally, although part of USEPA (2021h) rationale for dismissing ALT as an appropriate endpoint for RfD development was that the magnitude of PFOA and/or PFOS's effect on ALT was not large, this is also the case for the magnitude of changes associated with these PFAS for other human health endpoints such as increased cholesterol and decreased birth weight. As noted above, PFOA and PFOS are associated with increased incidence of clinically defined abnormal values for these endpoints. Furthermore, USEPA SAB (2022) noted that PFOA and PFOS cause increased ALT in laboratory animals, providing support for the conclusions that it is "a reproducible and rigorous endpoint that is predictive of adverse health effects."

In addition, USEPA SAB (2022) cited numerous studies of associations of elevated ALT with disease endpoints, including studies in which relatively small (<2-fold) increases in serum ALT were associated with "pathology-confirmed liver disease," such as non-alcoholic fatty liver disease (NAFLD). The SAB noted that the American Association for the Study of Liver Diseases Kim et al., 2008) has stated that serum ALT may be a predictor for overall health and mortality and that the American College of Gastroenterology (ACG; Kwo et al., 2017) has stated that elevated ALT is associated with increased liver-related mortality.

USEPA SAB (2022) also cited a recent systematic review of PFAS and hepatic effects (Costello et al., 2022) that identified 86 human epidemiology studies and 26 laboratory animal studies that assessed markers of liver injury (ALT, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, or steatosis). In many of these studies, increased ALT was associated with general population range exposures to PFOA and/or PFOS. Costello et al. (2022) concluded that "exposure to both PFOA and PFOS is associated with increased ALT in humans and that both compounds cause increased ALT and steatosis in rodents." Additionally, USEPA SAB (2022) cited several recent studies and reviews that suggest that non-alcoholic fatty liver disease may be associated with exposure to PFOA and PFOS and that more research on this question is needed. The Health Effects Subcommittee notes that several recent studies not cited by USEPA (2021a,b) or USEPA SAB (2022) provide further support for associations of increased ALT with PFOA

and PFOS in adults (Liu et al., 2022) and with maternal exposure to PFOA in children (Midya et al., 2022).

Birth weight

USEPA (2016a) reviewed 14 studies (9 general population; 5 from communities with contaminated drinking water) of associations of maternal serum PFOA and decreased birth weight. Similarly, USEPA (2016b) considered 9 studies (8 with general population level exposures; 1 occupational) that evaluated maternal serum PFOS and decreased birth weight. USEPA (2106a,b) also considered the conclusion of Verner et al. (2016) that associations of decreased glomerular filtration rate (GFR) with both increased maternal serum PFAS and decreased birth weight may explain part, but not all, of decrease in birth weight associated with PFOA and PFOS. USEPA (2016a, b) concluded that the available data suggest an association of PFOA and PFOS and decreased birth weight, and that this association cannot be totally explained by low GFR.

For PFOA, DWQI (2017a) reviewed meta-analyses (Johnson et al., 2014; Verner et al., 2015) that provide numerical estimates of the decrease in birth weight associated with increases in maternal serum PFOA. DWQI (2017a) also reviewed the Verner et al. (2016) evaluation of the impact of decreased GFR on this association. DWQI (2017) concluded that "confounding by GFR does not account for the major portion of the decrease in fetal growth that is associated with PFOA."

For PFOS, DWQI (2018) reviewed seven studies of maternal serum PFOS and birth weight and concluded that "although there is a suggestion of a relationship between maternal PFOS exposure and decreased birthweight from epidemiological studies, the evidence is not consistent." DWQI (2018) noted that there was a relatively narrow exposure range in the available studies and that "these observations therefore do not rule out an association at higher levels of PFOS exposure or more subtle effects in pregnancies at increased risk for low birthweight."

Numerous epidemiological studies of PFAS included in USEPA (2021a,b) that were published after the DWQI (2017a, 2018) evaluations provide additional support for associations of PFOA and PFOS with decreased weight at birth. In addition to the additional studies evaluating numerical changes in weight at birth, USEPA (2021a,b) also reviewed studies of PFOA and PFOS and LBW and SGA. Few or no studies of associations of PFAS and these endpoints were available when the DWQI (2017a, 2018) evaluations were performed.

USEPA (2021a) reviewed 10 studies published between 2016 and 2020 that evaluated associations of PFOA and "dichotomous fetal growth restriction endpoints" (SGA or related endpoints and/or LBW). Five of these studies were classified by USEPA as high confidence, three as medium confidence, and two as low confidence. Five of the seven studies that evaluated SGA showed an association with PFOA; the magnitude of the effects was generally consistent although not always statistically significant. Additionally, two of the four studies that evaluated

LBW showed some evidence of association with PFOA either overall or in one sex, although the associations were not statistically significant in some cases. USEPA (2021a) concluded that:

> "Overall, seven of the ten different studies examining either SGA or LBW or both showed some increased risks with increasing PFOA exposures. The magnitude of the associations was typically from 1.2 to 2.8 with limited evidence of exposure-response relationships among the categorical studies. Although the number of studies was small, few discernible patterns across study characteristics or confidence were evident across the SGA or LBW findings. Collectively, the majority of SGA and LBW studies were supportive of an increased risk with increasing PFOA exposures."

Similarly, USEPA (2021b) reviewed 9 studies published between 2017 and 2020 that evaluated associations of PFOS and SGA or related endpoints and/or LBW. These nine studies included all except one of the 10 studies of PFOA and SGA and/or LBW reviewed by USEPA (2021a). Four of the six studies that evaluated SGA showed an association with PFOS; the magnitude of the effects was generally consistent although not always statistically significant. Additionally, three of the four studies that evaluated LBW showed some evidence of an association with PFOA either overall or in one sex, although the associations were not statistically significant in some cases. USEPA (2021b) concluded that: "Collectively, the majority of SGA and LBW studies were supportive of an increased risk with increasing PFOS exposures."

USEPA SAB (2022) agreed with USEPA (2021a,b) that there is consistent evidence for association with PFOA and PFOS and decreased birth weight and related parameters. The Health Effects Subcommittee notes that these associations have generally been observed within the general population exposure range.

The recent studies of clinically defined indicators of decreased birth weight (LBW, SGA) and the USEPA (2021a,b) conclusions summarized above are notable because the biological and clinical significance of the relatively small decreases in birth weight associated with PFOA and PFOS have been previously subject to debate. The Health Effects Subcommittee (DWQI, 2017a) disagreed with the conclusion that such relatively small changes are not meaningful, stating that even small changes are "of public health concern because population-level changes of this magnitude will result in a shift in the overall distribution of values such that the number of individuals with clinically abnormal values is increased," and that "relatively small decreases in birth weight may be an indication of changes in other more subtle developmental parameters which were not assessed." As discussed above, the recent studies showing associations of PFOA and PFOS with clinically defined indicators (SGA, LBW) further support the biological and clinical significance of the effects of PFOA and PFOS on fetal growth.

Serum Lipids – Increased Cholesterol

For both PFOA and PFOS, evidence is stronger for an association with increased total cholesterol than for other serum lipids (HDL, LDL, triglycerides). For this reason, information on total cholesterol, but not other lipids, is reviewed in this section.

For PFOA, USEPA (2016a) reviewed 17 studies of total cholesterol, including 7 occupational studies, 5 studies of communities with elevated exposure through drinking water, and 5 general population studies (including one in adolescents and one in pregnant women). USEPA (2016a) concluded that there is a consistent association of serum PFOA and increased total cholesterol.

For PFOS, USEPA (2016b) reviewed two occupational studies and 12 studies with general population level exposure (including one in pregnant women, and five in children or adolescents) that evaluated associations with total cholesterol. USEPA (2016b) concluded that "overall, the epidemiologic evidence supports an association between PFOS and increased total cholesterol."

For PFOA, DWQI (2017a) reviewed 20 studies that evaluated total serum cholesterol and two studies that evaluated clinically defined high cholesterol. There was evidence of an association with increased cholesterol in seven general population studies, three very large studies of highly exposed community populations, and three case-control occupational studies. In general, studies of the general population, as well as large, mid-exposure range community studies and occupational studies with longitudinal designs, found consistent evidence of an association, while a few smaller, higher exposure range community and occupational studies found no evidence. None of the 20 studies evaluated found evidence of an inverse association.

DWQI (2017a) discussed that the exposure-response relationship for PFOA and increased cholesterol is generally steepest at low serum PFOA levels and is less steep, approaching a plateau, at higher serum PFOA levels. It was noted that, for this reason, associations may not be observed in study populations with higher exposures, such as a highly exposed community or occupationally exposed workers, since even the comparison group (e.g., the intended control group) may have exposures high enough to fall on the much flatter portion of the exposure-response curve.

DWQI (2017a) concluded that: "In summary, the epidemiologic database for serum cholesterol and PFOA, which included twenty studies, provides evidence of consistency, strength and dose-response, including some evidence of temporality. Associations with clinically defined hypercholesterolemia were reported in some studies. These findings provide evidence supporting a causal relationship between PFOA and serum cholesterol."

DWQI (2018) reviewed ten studies of serum PFOS. Eight of these studies showed significant associations within the general population exposure range, and another showed a non-significant trend of increasing serum cholesterol. A study in occupationally exposed workers also reported a statistically significant association of total cholesterol and PFOS. Another study found a significant positive association between clinically defined hypercholesterolemia and serum PFOS. DWQI (2018) concluded that: "There is, therefore, strong evidence for a positive association of PFOS exposure and increased serum total cholesterol even at relatively low levels of PFOS exposure."

USEPA (2021a) reviewed 43 human studies of PFOA and serum lipids that were not considered by USEPA (2016a). Of these 43 studies, four (including two occupational studies) were

considered by DWQI (2017a) and 39 were not. The 11 studies of PFOA and total cholesterol in children generally found positive associations, although they were not consistently statistically significant. The two studies in pregnant women both found a statistically significant association with increased serum cholesterol. Of the 13 general population studies, positive associations with increased total cholesterol or hypercholesteremia were reported in six of eight studies judged to be of medium confidence and seven of nine studies judged to be of low confidence. USEPA (2021a) concluded that the evidence generally supports an association of PFOA and increased serum cholesterol, but that there were some inconsistencies.

USEPA (2021b) reviewed 42 human studies of PFOS and serum lipids that were not reviewed by USEPA (2016b). Of these 42 studies, only one occupational study was included in the DWQI (2018) review. The USEPA (2021b) review of ten studies of PFOS and increased serum cholesterol in children concluded that a positive association was supported, and two studies in pregnant women also reported an association with serum total cholesterol. In the general population, 14 of 16 studies showed a positive association with serum total cholesterol. There were only three occupational, all of which were judged to be of low quality, and they did not provide consistent results. USEPA (2021b) concluded that "the available evidence supports a positive association between PFOS and total cholesterol in the general population, including children and pregnant women."

USEPA SAB (2022) agreed with the USEPA (2021a,b) conclusions that the weight of evidence supports an association of serum PFOA and PFOS with serum cholesterol and provided critical comments on several aspects of those evaluations, as follows.

USEPA SAB (2022) commented on the USEPA (2021a) review of serum PFOA and total cholesterol in occupationally exposed workers. The SAB noted that USEPA (2021a,b) only reviewed studies not included in the earlier USEPA (2016a,b) evaluations, and that this approach does not consider the entire weight of evidence for the effect being evaluated. Specifically, USEPA (2021a) reviewed only three occupational studies of serum PFOA and total cholesterol (two of which were also reviewed by DWQI, 2017a) that did not find associations of PFOA with total cholesterol, all three of which were judged to be of low quality, and did not find associations with increased serum cholesterol. However, USEPA (2016a) reviewed seven additional occupational studies of PFOA and serum cholesterol, some of which may have been of higher quality, and found generally consistent associations. USEPA SAB (2022) noted that USEPA (2021a) stated that the new studies that they reviewed "suggest no association between PFOA and TC [total cholesterol] in workers" and that "differences in findings from occupational studies between [USEPA, 2016a] and this review may be attributable to the limitations of occupational studies in this review." USEPA SAB (2022) concluded that "there does not appear to be a supportable rationale for making a conclusion based on only three low confidence studies when other potentially stronger studies are also available."

Additionally, USEPA SAB (2022) commented on consideration of Convertino et al. (2018) by USEPA (2021a), which contributed to the USEPA (2021a) conclusion of inconsistencies in the general population evidence for PFOA. Convertino et al. (2018) is a study, rated as low

confidence by USEPA (2021a), that reported decreased total cholesterol in advanced cancer patients given very high doses of PFOA. Problematic issues with the inclusion of this study in the USEPA (2021a) review were noted by USEPA SAB (2022), and the SAB concluded that, while decreased serum cholesterol was reported in the subjects with the highest plasma PFOA levels, this study "does not appear to be appropriate for consideration in hazard identification of PFOA."

USEPA SAB (2022) cited the concerns presented in NJDEP (2020), which states that Convertino et al. (2018) "is not useful in the evaluation of potential health effects of chronic drinking water exposure to PFOA in the general population" and that "limitations of this study include small sample size, very short length, limited power of study, and potential altered metabolic state of study group consisting of late-stage cancer patients. Observations in these patients cannot be considered relevant to healthy individuals because their nutritional and physiological status was likely affected by their severe illness." The USEPA SAB (2022) also noted that an earlier abstract about this study (Macpherson et al., 2010) reported that "one of the patients dosed with PFOA experienced drug related toxicity (DLT) consisting of 'grade 5 renal failure and transaminitis' (indicative of liver damage)." However, these observations, which indicate the potential for PFOA to cause renal and hepatic toxicity in humans, were not mentioned by Convertino et al. (2018).

USEPA SAB (2022) further noted that "the plasma PFOA levels in the subjects in this study [Convertino et al., 2018] were extraordinarily high" (~4000 ng/ml to ~630,000 ng/ml), and that "cholesterol was decreased only in the three highest exposure categories (approximately 262,000 ng/ml or higher plasma PFOA), but not in the seven lower exposure categories that also had extremely high plasma PFOA levels. As stated by USEPA SAB (2022): "The plasma PFOA levels at which cholesterol was decreased are many orders of magnitude above those found in the general population or in communities with contaminated drinking water. They are higher than the highest serum or plasma PFOA levels [reported] in occupationally exposed workers…, and they are similar to the serum PFOA levels at which cholesterol is decreased in animal studies, presumably through activation of PPAR-alpha. The observation of decreased cholesterol at these extremely high plasma concentrations is consistent with the effects of PPAR-alpha activating drugs that reduce serum cholesterol in humans. In contrast, the increased cholesterol associated with PFOA in the general population and in individuals exposed through contaminated drinking water likely occurs through a different mechanism that is operational at much lower PFOA concentrations."

Cancer

Kidney and testicular cancer

Bartell and Vieira (2020) identified seven epidemiological studies of PFOA and kidney cancer. They concluded that "the available studies on PFOA and kidney cancer clearly meet Hill's criteria of strength of the association, consistency, temporality, biological gradient, and biological plausibility/coherence. Thus, the evidence is sufficient to indicate that PFOA is most likely a cause of kidney cancer in humans." They also reviewed the limited number of

epidemiological studies (three) of testicular cancer and PFOA, and concluded that "the available studies on PFOA and testicular cancer clearly meet Hill's criteria of strength of the association, temporality, and biological plausibility/coherence. … indicat[ing] that PFOA is most likely a cause of testicular cancer in humans."

As noted above, USEPA (2021a) developed draft CSFs of 14,380 $(mg/kg/day)^{-1}$ (central tendency estimate) and 29,300 $(mg/kg/day)^{-1}$ (95^{th} percentile upper confidence limit) from dose-response data for the association of increased risk of renal cell carcinoma with serum PFOA levels in the U.S. general population (Shearer et al., 2021). California EPA (2021) developed a central tendency estimate CSF of 2600 $(mg/kg/day)^{-1}$ for PFOA based on the geometric mean of the CSFs for kidney cancer for the data from two studies: 1) 6370 $(mg/kg/day)^{-1}$ from Shearer et al. (2021), based on NHANES data; and 2) 1050 $(mg/kg/day)^{-1}$ from Vieira et al. (2013), based on the C8 Health Study population with exposure to PFOA-contaminated drinking water. USEPA (2021a) and California EPA (2021) used inverse variance weighted regression modeling to develop these CSFs. The USEPA (2021a) and California EPA (2021) CSFs from Shearer et al. (2021) in terms of serum PFOA $(ng/ml)^{-1}$ are identical, 0.00178 $(ng/ml)^{-1}$ (central tendency estimate). The difference in CSFs in terms of administered dose (California EPA - 6370 $[mg/kg/day]^{-1}$; USEPA – 14,380 $[mg/kg/day]^{-1}$) results from the use of a higher clearance factor of 0.28 ml/kg/day by California EPA than the one used by USEPA, 0.12 ml/kg/day. The USEPA SAB (2022) agreed that human data should be considered as the basis for the PFOA CSF, but recommended that USEPA consider CSFs based on other studies in addition to Shearer et al. (2021).

More recently, Steenland et al. (2022) performed a pooled analysis of individual-level serum PFOA concentrations and kidney cancer from a study of the general population study (Shearer et al. (2021) and a study of a population with elevated PFOA exposure from contaminated drinking water from the C8 Health Study (Barry et al., 2013). Steenland et al. (2022) selected these two studies because they concluded that they had the best quantitation of serum PFOA concentrations of the seven studies of PFOA and kidney cancer included in an earlier review by Bartell and Vieira (2020). Steenland et al. (2022) state that: "Although inverse weighted regression is an accepted approach for evaluating average dose–response trends across exposure categories in different studies…, pooled individual-level data provide the best opportunity to examine the shape of the dose–response curve."

Based on their analysis of the pooled data, Steenland et al. (2022) developed a CSF in terms of serum PFOA of 0.00179 $(ng/ml)^{-1}$ (central tendency estimate), which is essentially identical to the serum level CSF for Shearer et al (2021) of 0.00178 $(ng/ml)^{-1}$ (central tendency estimate) developed by USEPA (2021a) and California EPA (2021). Steenland et al. (2022) developed a CSF in terms of administered dose of 12,800 $(mg/kg/day)^{-1}$ from the serum level CSF using a clearance factor of 0.14 ml/kg/day. This CSF is close to the USEPA (2021a) CSF (central tendency estimate) of 14,380 $(mg/kg/day)^{-1}$ which is based on an almost identical serum level CSF and a similar clearance factor of 0.12 ml/kg/day.

Liver cancer

The potential for PFOA and/or PFOS to increase the risk of liver cancer in humans is of interest because these PFAS are associated with ALT, a marker of liver damage in humans, and they cause hepatic toxicity and liver tumors in rodents. Additionally, as reviewed by Goodrich et al. (2022), PFOA, PFOS, and other PFAS have been associated with biomarkers consistent with non-alcoholic fatty liver disease. However, until recently, epidemiological studies that focus specifically on liver cancer and PFAS have not been available. Two relevant studies that were not considered by USEPA (2021a,b) have recently become available and are summarized below.

Goodrich et al. (2022) conducted a nested case-control study of serum PFAS and non-viral hepatocellular carcinoma (HCC). The study included 50 cases and 50 controls individually matched by age, sex, race/ethnicity, and study area from the Multiethnic Cohort, a prospective cohort of >200,000 California and Hawaii residents from a variety of racial/ethnic groups. PFAS and the metabolome were analyzed in plasma samples taken prior to cancer diagnosis. Geometric mean plasma concentrations of PFOA, PFOS, PFNA, PFHxS, and PFDA were similar in cases and controls. However, for PFOS the plasma levels at or above the 90th percentile in the 1999-2000 NHANES (>55 ng/L, equal to the 85th percentile in this study) were associated with a statistically significant 4.5-fold increased risk of HCC. While the authors did not state the number of cases who fell into this high PFOS exposure category, there would be 15 subjects (including cases and controls), based on high PFOS being defined as at or above the 85th percentile. In other statistical analyses of plasma PFOS and HCC risk, there was a positive association that was not statistically significant (OR 1.2; 95% CI 0.91-1.60) for plasma PFOS analyzed as a continuous variable. Analysis using ordinary logistic regression controlling for matching variables (age, sex, ethnicity, and study site) showed a similar statistically significant association between high plasma PFOS and HCC similar to the main analysis (OR 4.4; 95% CI 1.2-20.00). When BMI was included as a variable, the association of HCC with PFOS was not statistically significant (OR 2.90; 95% CI 0.78-10.0), while it did remain significant (OR 5.70; 95% CI 1.1-30.00) when baseline diabetes mellitus (accounting for 38% of the cases) included in the regression.

Because high plasma PFOS was associated with statistically significant increased risk of hepatocellular cancer, Goodrich et al. (2022) conducted metabolome-wide association studies (MWAS) to investigate associations between the metabolome (i.e., levels of metabolites/small molecules) in blood plasma and plasma PFOS and/or HCC. MWAS was not performed for other PFAS. MWAS identified numerous metabolites and enriched metabolic pathways associated with high PFOS exposures and/or HCC. Four metabolites (glucose; butyric acid, a short-chain fatty acid; a-ketoisovaleric acid, a branched-chain a-keto acid; 7a-hydroxy-3-oxo-4-cholestenoate, a bile acid) and enrichment of five metabolic pathways, including pathways related to amino acid and glycan biosynthesis, were associated with both high PFOS and HCC. The authors discuss that these metabolites may play a role in the etiology of metabolic disorders and liver disease including HCC.

An additional recent study, Cao et al. (2022) also reported an association of PFOS with increased risk of liver cancer (type not specified) in a Chinese study population (203 cancer patients, 203 controls). Serum PFAS was measured after cancer diagnosis. Serum levels of PFOS and 6:2 chloro-polyfluoroalkyl ether sulfonic acid, a replacement for PFOS widely used in China, were significantly associated with increased risk of liver cancer after adjustment for various covariates, with odds ratios reported by the authors as 2.609 (CI 1.179-4.029) and 1.844 (CI 1.176, 2.512), respectively, for each log unit increase. The odds ratio for HCC was also significantly increase for PFOA, although the increase was very small (1.036, CI 1.002, 1.070) and the p for trend (0.07) was not significant. Associations with other PFAS were not statistically significant.

Overall mortality

A recent study by Wen et al. (2022) reports increased overall mortality, cardiovascular mortality, and cancer mortality associated with PFAS, especially PFOS, in adults (age $\geq$ 18 years) who participated in NHANES from 1999 to 2014. Mortality of NHANES (1999-2014) participants was determined through the end of 2015. The study group included 11,747 subjects who had NHANES serum data for the seven PFAS (PFOA, PFOS, PFNA, PFHxS, PFDA, PFDoA [perfluorododecanoic acid], and MeFOSA [N-methyl perfluorooctane sulfonamide]) that were measured in 1999-2014 and were detected in at least 10% of NHANES participants. Mortality analyses were based on tertiles (i.e., high, medium, low) for total PFAS, total PFAS minus PFOS, total PFAS minus PFOA, as well as tertiles of PFOA and PFOS. For both total PFAS and PFOS, hazard ratios (HRs) for mortality from all causes, heart disease mortality, and cancer mortality was significantly higher in the high exposure group compared to the low exposure group. This was true both for unadjusted HRs and HRs adjusted for multiple potential confounders. These associations remained for total PFAS with PFOA excluded, but they were not found for total PFAS with PFOS excluded. As noted by the authors: "Limitations of this study include the potential for unmeasured confounding, selection bias, a relatively small number of deaths, and only measuring PFAS at one point in time. Further studies with serial measures of PFAS concentrations and longer follow-ups are necessary to elucidate the association between PFAS and mortality from specific causes."

Duration of breastfeeding

As reviewed in DWQI (2017a), low doses of PFOA cause delayed mammary gland development in mice. However, there are insufficient data to determine whether the delays in mammary gland development cause impaired lactational function in mice.

In contrast, while there are no data on the effects of PFAS on mammary gland development in humans, the DWQI (2017a) reviewed three studies from the general population in different locations (Denmark - Fei et al., 2010; U.S. - Romano et al., 2016; Faroe Islands -Timmermann et al., 2016) that reported associations of maternal PFOA exposure with shorter duration of breast feeding; no studies that were negative for this association were identified by the DWQI (2017a). Fei et al. (2010) and Timmermann et al. (2016) also reported an association with PFOS, although the association with PFOS in Timmermann et al. (2016) did not remain after adjustment for co-

exposure to other PFAS. In Romano et al. (2016) and Timmermann et al. (2016), each of which controlled for prior breastfeeding history, the association of serum PFOA during pregnancy and shorter duration of breast feeding remained after adjustment for previous breast feeding, indicating that the association was not due to reverse causality (i.e., longer previous breast feeding in multiparous women resulting in decreased serum PFAS levels).

Two additional studies (Timmermann et al., 2022b; Nielsen et al., 2022) that reported associations of PFAS with breast feeding initiation and/or duration were cited by USEPA SAB (2022). These studies became available after the DWQI (2017a) evaluation; no newer studies that are negative for this effect were identified by the Health Effects Subcommittee.

Timmermann et al. (2022b) found associations of PFOA, PFOS, and PFNA with shorter duration of breast feeding in Danish women from the general population. As was the case in Timmermann et al. (2016) and Romano et al. (2016), parity had no effect on this association. Timmermann et al. (2022b) noted that the associations were stronger when women who ceased breastfeeding for reasons other than insufficient lactation were omitted from the analysis, "supporting the hypothesis that the association between PFAS and reduced breastfeeding duration was limited to cases with insufficient lactation."

Nielsen et al. (2022) evaluated initiation and duration of breast feeding in women with elevated PFAS exposures from contaminated drinking water in Ronneby, Sweden. Blood samples taken from about 13% of the population in 2014-15 found the geometric mean blood serum concentrations of PFOA, PFOS, and PFHxS in women of childbearing age (21–40 years old) to be 5 ng/L, 80 ng/L, and 60 ng/L respectively, compared to 1.3 ng/L, 3.2 ng/L, and 0.9 ng/L in a comparison population from a community where drinking water was not contaminated. The study is based on information on breast feeding from health records for ~85% of children born in 1999-2009, prior to discovery of the drinking water contamination in 2013. Individual serum data were not available, and residential address before delivery was used as a proxy for exposure to high or low levels in drinking water. Women in Ronneby overall were twice as likely as those in the reference community to not initiate breastfeeding. The likelihood of not initiating breastfeeding was higher in both primiparous and multiparous women who were exposed to either high or low water levels (relative risks: 1.64 – 2.92). However, after adjustment for potential confounders, the 95% confidence intervals were wide and lacked statistical significance, potentially due to the small number of women who did not initiate breastfeeding in each group. The odds of ending exclusive breast feeding before 3 months and ending breastfeeding in general before 6 months were increased in primiparous, but not multiparous, women who were exposed to contaminated drinking water, with statistical significance for ending breast feeding before 6 months.

In summary, all five epidemiological studies that were identified found associations of PFAS with decreased lactational function. Four of these studies were in women from the general population, presumably without known exposure to PFOA or PFOS from drinking water, while one study is from a community with elevated PFAS exposures from contaminated drinking water. The negative effects on breast feeding in humans reported in these studies may

potentially be relevant to the toxicological data demonstrating that low doses of PFOA causes adverse effects on mammary gland development in mice. The occurrence of these effects within the general population exposure range further indicates the need to limit exposure to PFOA and PFOS in drinking water and provides support for Health-based MCLs for PFOA and PFOS below the current PQLs.

APPENDIX 4: CONSIDERATION OF HIGHER EXPOSURES TO PFOA AND PFOS IN DRINKING WATER IN INFANTS

Infants

Exposures to PFOA, PFOS, and other long-chain PFAS in breastfed infants are higher than in their mothers and other older individuals, both in the general population and in communities with contaminated drinking water (Lakind et al., 2022; Post, 2022). These higher exposures result from two factors: 1) concentrations of PFOA and PFOS in breast milk are higher than in maternal drinking water, and 2) infants consume more fluid than older individuals on a body weight basis. Because of their higher rate of fluid consumption, exposure to formula fed infants is also elevated when drinking water is contaminated. As reviewed below, conclusions about higher exposures to infants are further supported by information on PFAS concentrations in both infant blood serum and breast milk. These higher exposures are of concern because infants are sensitive subpopulations for the developmental effects of PFOA and PFOS and for other effects of these PFAS that result from early life exposures, such as decreased antibody response to vaccines (Grandjean et al., 2012; Abraham et al., 2020).

Serum PFAS concentrations in breastfed infants

In general, serum PFAS concentrations in breastfed infants are substantially higher than in their mothers. For example, Fromme et al. (2010) measured serum PFAS levels in mothers and their breastfed infants from the general population. Serum PFOA and PFOS levels in the breastfed infants were similar or lower than in their mothers at birth and then increased by several-fold between birth and 6 months of age (Figure A4.1; Table A4.1). For PFOA, serum levels at age 6 months were almost 4-fold higher than maternal serum levels.

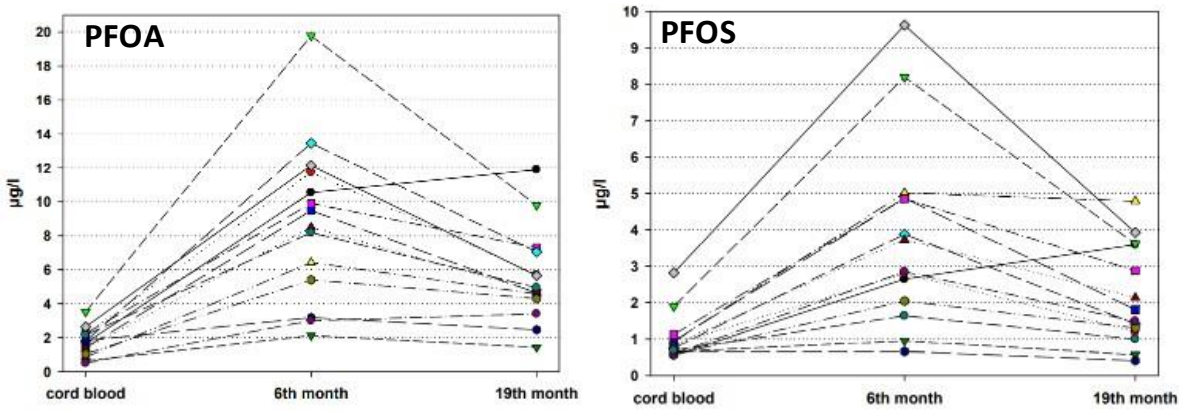

Figure A4.1. PFOA and PFOS serum levels in breastfed infants from the general population (Fromme et al., 2010).

Table A4.1. Comparison of median maternal and breastfed infant serum levels (ng/ml) of long-chain PFAS based on data from Fromme et al. (2010)*

Blood PFAS (ng/ml)	Maternal (at delivery; ng/ml)	Fetus/Infant							
		Cord (at birth)		6 months			19 months		
		ng/ml	% compared to maternal	ng/ml	% compared to maternal	% compared to at birth	ng/ml	% compared to maternal	% compared to at birth
PFOA	1.9	1.4	74%	6.9	**363%**	493%	4.6	**242%**	329%
PFOS	3.2	1.0	31%	3.0	94%	300%	1.9	59%	190%
PFNA	0.6	< 0.4	< 66%	1.0	**167%**	> 250%	0.6	100%;	> 150%
PFHxS	0.5	0.2	40%	0.6	**120%**	300%	0.6	**120%**	300%

*Note: Neither confidence intervals or tests of statistical significance were reported.

When drinking water is contaminated with PFOA and/or PFOS, exposures to all age groups (e.g., infants, children, adults) are higher than in the general population. Additionally, exposures to infants, including those who are breastfed and those who consume formula prepared with drinking water, are higher than in older individuals. This is the case because infants ingest more fluid (breast milk or formula) on a body weight basis than older individuals. Additionally and importantly, concentrations of PFOA and other long-chain PFAS (PFOS, PFNA, PFHxS) in breast milk are higher than in the mother's drinking water, with the highest predicted serum breast milk:drinking water ratios (8.3:1 - 9.1:1) for PFOA. The higher PFAS levels in breast milk than in the contaminated drinking water consumed by the breast-feeding mothers result in much higher PFAS exposures in breastfed infants than in infants fed with formula prepared with the same contaminated drinking water (Post, Cohn, Cooper, 2012; DWQI, 2017a; DWQI, 2018; Goeden, 2019; Post, 2022). Information on the predicted relationships between concentrations of concentrations of long-chain PFAS drinking water, adult (e.g., maternal) blood serum, and breast milk is shown in Table A4.2.

Table A4.2. Predicted relationships between concentrations of concentrations of long-chain PFAS drinking water, adult (e.g., maternal) blood serum, and breast milk.

	Adult Blood Serum:Drinking Water Ratio (a)[a]	Breast Milk:Blood Serum Ratio (b)[b]	Breast Milk:Drinking Water Ratio (a x b)
PFOA	114:1 ($t_{1/2}$ = 2.3 years) [c]	0.073:1	8.3:1
	124:1 ($t_{1/2}$ = 2.7 years) [d]		9.1:1
PFOS	197:1 ($t_{1/2}$ = 5.4 years) [c]	0.013:1	2.6:1
	124:1 ($t_{1/2}$ = 3.4 years) [d]		1.6:1
PFNA	200:1[c]	0.03:1	6.0:1
PFHxS	200:1[e]	0.013:1	2.6:1

[a] Ratios are based on average drinking water ingestion rate for women of childbearing age and pregnant women (0.016 L/kd/day). Use of the higher average ingestion rate for lactating women (0.023 L/kg/day) would result in higher ratios.

[b] Ratios are from LaKind et al., 2022.

[c] Ratios are from DWQI (2015, 2017a, 2018). Sources of half-lives ($t_{1/2}$) are Bartell et al. (x) for PFOA and Olsen et al. (2007) for PFOS. Ratio for PFNA was estimated as explained in DWQI (2015).

[d] Half-lives used by USEPA (2021a,b) from Li et al. (2018).

[e] Calculated from half-live and volume of distribution provided by NHDES (2019).

The Health Effects Subcommittee recognized the higher PFOA exposures in infants, particularly those that are breastfed, in its early work including in its 2010 internal draft Health-based MCL Support Document (DWQI Health Effects Subcommittee, 2010) and in a peer-reviewed publication by current Subcommittee members (Post, Cohn, Cooper, 2012). When developing Health-based MCLs for PFOA and PFOS, the Health Effects Subcommittee (DWQI, 2017a, 2018) emphasized concerns about potential adverse effects from the higher exposure to infants, particularly those that are breastfed. However, at the time when the DWQI Health-based MCLs were developed, models for quantitatively considering PFOA and PFOS exposure to the breastfed infant were not yet available. In recognition of the need to consider the higher exposures to infants, DWQI (2017a, 2018) stated: "Additionally, the default RSC [Relative Source Contribution factor] of 20%, while not explicitly intended for this purpose, also partially accounts for the greater [PFOA and PFOS] exposures to infants who are breast-fed or consume formula prepared with contaminated drinking water, as compared to older individuals. These higher exposures during infancy must be considered because short term exposures to infants are relevant to the effects of concern (delayed mammary gland development and increased relative liver weight [for PFOA]; decreased immune response [for PFOS])."

After the Health Effects Subcommittee had completed its development of Health-based MCLs for PFOA and PFOS, a transgenerational toxicokinetic model to predict early-life exposures to PFAS from contaminated drinking water was developed by the Minnesota Department of Health and published in a peer-reviewed journal (Goeden et al. 2019). This model considers transplacental exposure to the fetus resulting from maternal consumption of PFAS-contaminated drinking water, exposure from birth until age one year via breast milk or formula prepared with PFAS-contaminated water, and continued exposure from PFAS-contaminated water from early childhood through adulthood (Figure A4.2). For example, peak serum PFOA levels in breastfed

infants resulting from maternal consumption of PFOA in drinking water are predicted to be six times higher than in adults who consume water with the same PFOA concentration.

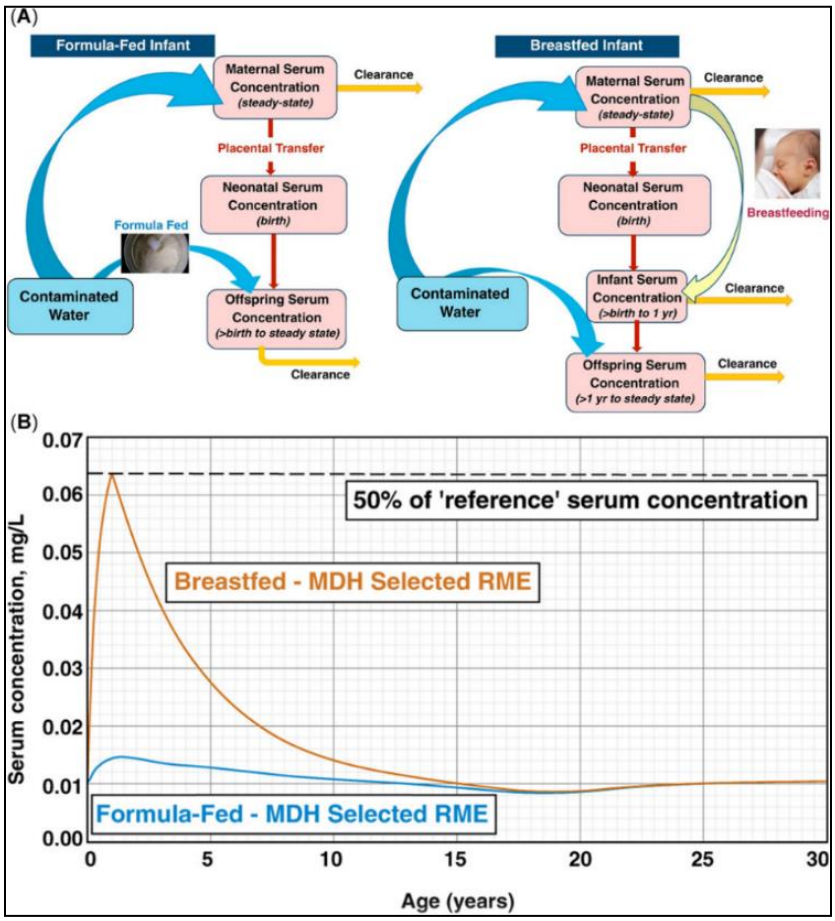

Figure A4.2. Toxicokinetic model for transgenerational to PFOA from drinking water. (A) Conceptual representation of the model for formula-fed and breastfed infant exposure scenarios. (B) Predicted serum levels from drinking water at the Minnesota guideline level of 35 ng/L. MDH=Minnesota Department of Health; RME=reasonable maximum exposed (Goeden et al. 2019).

USEPA (2021a,b) also considered the higher exposures to breastfed infants for development of PODs for effects caused by prenatal and/or early life exposure using a model developed by Verner et al. (2016). USEPA SAB (2022) strongly supported use of a model to consider prenatal and early life exposure. However, it questioned whether the Verner et al. (2016) model is appropriate for development of health-based drinking water levels (e.g., MCLGs) and recommended that USEPA consider using Goeden et al. (2019) model instead. As noted by USEPA SAB (2022): "…the two models [Verner et al., 2016; Goeden et al., 2019] have different purposes and provide different information. The Verner et al. (2016) model predicts infant and child serum PFOA or PFOS levels resulting from a constant daily PFOA or PFOS dose (ng/kg/day) to the mother and to the child after weaning. However, it is not clear how a RfD from the Verner et al. (2016) model, which predicts serum PFOA or PFOS levels at age 5 years from a constant daily dose to the mother and the child, can be used to develop an MCLG that

considers both exposure through breastfeeding, post-weaning and changing drinking water consumption rates up to age 5. In contrast, the Goeden et al. (2019) model considers both age-specific toxicokinetic factors and the changing drinking water intakes at different age periods [e.g., maternal, infant, children of different ages] … and predicts the serum PFOA or PFOS levels at any age (including infancy, childhood, and adulthood) that result from maternal and child consumption of drinking water with a certain concentration (ng/L) of PFOA or PFOS."

The Goeden et al. (2019) model has been used, along with state-specific RfDs, by Minnesota and at least three 3 other states (Michigan, New Hampshire, and Washington) to develop health-based drinking water standards for PFOA and PFOS (reviewed in Post, 2021). It is noted that the health-based drinking water standards developed with the Goeden et al. (2019) model have used an infant-specific RSC of 50% that is 2.5-fold less stringent (i.e., resulting in a 2.5-fold higher drinking water value) than the default RSC of 20% used by DWQI (2017a, 2018). All other factors (e.g., RfDs, clearance factor) being equal, health-based drinking water concentrations developed with the Goeden et al. (2019) model are lower than with the default approach of a constant adult drinking water ingestion rate.

Health-based MCLs using the Goeden et al. (2019) model (including an RSC of 50%) with the RfDs (2 ng/kg/day for PFOA; 1.8 ng/kg/day for PFOS) and clearance factors from DWQI (2017a, 2018) are estimated as 3.9 ng/L for PFOA, slightly below the New Jersey PQL of 6 ng/L, and 11 ng/L for PFOS, somewhat above the New Jersey PQL of 4 ng/L for PFOS. Use of lower RfDs based on human data would result in even lower Health-based MCLs. These estimated Health-based MCLs that consider exposure to breastfed infants further support the conclusion that Health-based MCLs below the NJ PQLs are appropriate.

The Health Effect Subcommittee compared peak serum PFOA concentrations in breastfed infants (Goeden et al., 2019) at several drinking water concentrations to the range of No Observed Adverse Effect Concentration (NOAEC) serum PFOA levels (12.2 to 16.9 ng/ml) for decreased antibody response to three different vaccines in one year old children (Abraham et al., 2020) (Figure 5).[9] It should be noted that this analysis is intended as an example, and that it is based on serum-level NOAECs for PFOA from Abraham et al. (2020) because the required data were provided in the publications, not because the NOAECs from this study are necessarily the most sensitive effects of PFOA.

The total serum PFOA concentrations in adults shown in Figure A4.3 represent the sum of the general population median of 1.47 ng/ml (NHANES, 2017-18) and the predicted increase in serum PFOA based on a serum:drinking water ratio of 114:1 for average drinking water ingestion of 0.016 L/kg/day (DWQI, 2017a). The peak serum PFOA concentrations in breastfed infants shown in Figure A.4.3 are six-fold higher than the total adult serum concentrations (Goeden et al., 2019).

[9] This analysis is based on an earlier analysis conducted by NJDEP Division of Science and Research in July 2021.

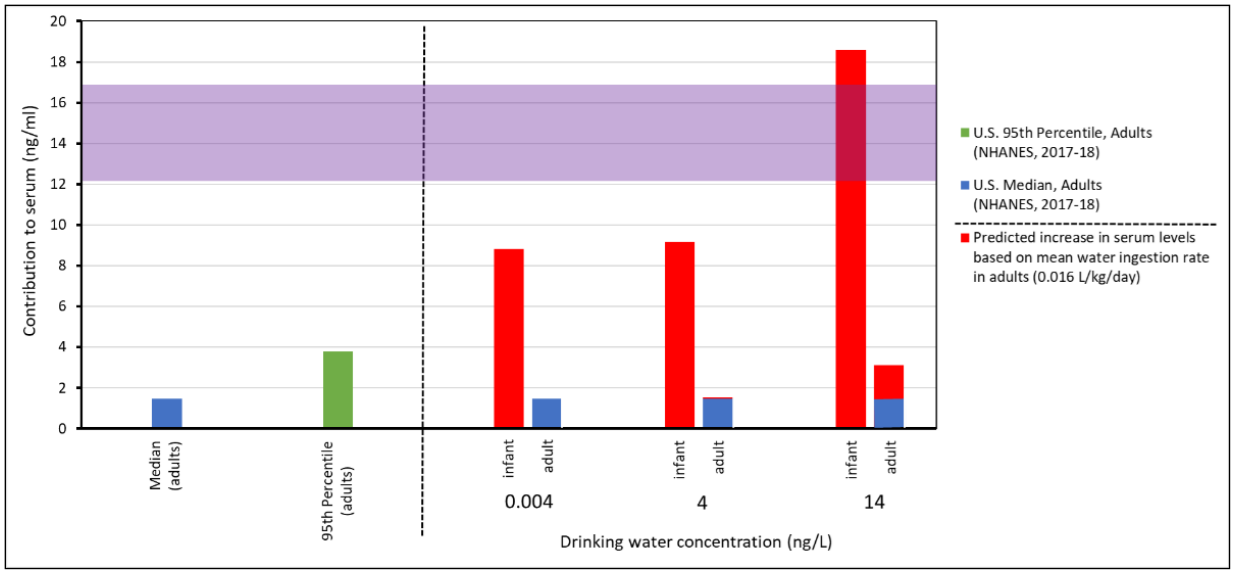

Figure A4.3. Predicted serum PFOA concentrations in adults and breastfed infants from average (0.016 L/kg/day) consumption of drinking water contaminated with various concentrations of PFOA. The calculations used to determine these serum concentrations are described in the text. The purple horizontal bar represents the range of No Observed Adverse Effect Concentrations (NOAECs) serum PFOA levels (12.2 to 16.9 ng/ml) for decreased antibody response to three different vaccines in one year old children (Abraham et al., 2020). This analysis is based on an earlier analysis conducted by NJDEP Division of Science and Research in July 2021.

As shown in Figure A.4.3, serum PFOA concentrations in infants whose mothers consume drinking water with 14 ng/L PFOA at an average rate are predicted to exceed the NOAECs for decreased vaccine response. As mentioned above, these predictions are based on average drinking water consumption and serum PFOA levels would be higher with greater than average water consumption. It should also be noted that these NOAECs do not include the 10-fold uncertainty factor for intra-individual variability that was applied in the draft USEPA (2021a,b) RfDs based on human data. If this uncertainty factor were applied, the range of target human serum levels would be 1.2 to 1.69 ng/ml, far below the infant serum PFOA level predicted even with essentially no (0.004 ng/L) exposure to PFOA in drinking water. This analysis provides further support for a Health-based MCL for PFOA below the New Jersey PQL of 6 ng/L.

PFAS concentrations in breast milk

As reviewed below, studies of measured and modeled PFAS concentrations in human breast milk indicate elevated exposures to breastfed infants even in the general population with little or no exposure through drinking water.

DWQI (2017a) reviewed available data on PFOA in human breast milk in studies from locations worldwide and stated that: "Concentrations in breast milk were generally similar in studies from different parts of the world. In studies using sensitive analytical methods enabling detection of lower concentrations, median PFOA levels were 36 ng/L (Massachusetts; Tao et al., 2008a), 67 ng/ml (Japan; Tao et al., 2008b), and 46 ng/L (China; Liu et al., 2010), while PFOA was not

detected or was infrequently found in breast milk in some other studies with higher detection limits…. PFOA was frequently found in breast milk at concentrations higher than 40 ng/L, with some detections exceeding 100 ng/L (for example, in Belgium; Roosens et al., 2010)."

Similarly, DWQI (2018) stated: "PFOS has been detected in human breast milk in studies from locations worldwide. ATSDR (2015) summarized data from studies from Massachusetts, Sweden, Germany/Hungary, and China published between 2006 and 2008. Concentrations in breast milk were generally similar in these studies from different parts of the world. PFOS was detected in almost all samples, with minimum concentrations in the four studies ranging from <32 - 60 ng/L, and maximums ranging from 360-639 ng/L."

Fromme et al. (2022) recently reviewed worldwide data on PFAS in breast milk, including many but not all of the studies reviewed by DWQI (2017a, 2018) and additional more recent studies (Table A4.3). Additionally, LaKind et al. (2022) recently reviewed available monitoring data for PFAS in breast milk in North America (U.S. and Canada). Only two papers that reported levels of PFAS in breast milk in the U.S. were identified (Tao et al., 2008a; Zheng et al., 2021); both of these are included in Table 6 from Fromme et al. (2022). An additional U.S. study, von Ehrenstein et al. (2009), does not provide useful data because the detection levels were too high to detect PFAS in the breast milk samples.

Reference	N	PFOS		PFOA		PFHxS		Country, year
		% > LOQ	Median (Min-Max)	% > LOQ	Median (Min-Max)	% > LOQ	Median (Min-Max)	
Europe								
This study	180	31	<25 (<25–248)	53	<25 (<25–326)	0	<75	Germany, 2016/17
Serrano et al., 2021	82	34	<0.9 (<0.9–65)	84	7.2 (<0.9–252)	24	<0.7 (<0.7–45)	Spain, 2015–18
Cerna et al., 2020	232	99	14[c] (<2–83)	100	24[c] (<3–160)	–	–	Czech Rep., 2017
Awad et al., 2020	10	25	39[d] (23–58)	25	42[d] (<2–81)	20	7[d] (<4–13)	Sweden, 2016
Abdallah et al., 2020	16[a]	62	20 (<20 – 120)	100	100 (16–350)	31	<40 (<40–87)	Ireland
Beser et al., 2019	20	55	69 (<66–78)	85	138 (<133–180)	–	–	Spain
Motas Guzmàn et al., 2016	67	–	–	60	26 (<10 – 211)	–	–	Spain, 2014
Cariou et al., 2015	61	31	- (<40–376)	18	- (<50–308)	15	- (<6–22)	France, 2010–13
Barbarossa et al., 2013	21	90	57[d] (<15–288)	81	76[d] (<24–241)	–	–	Italy, 2010
Lankova et al., 2013	50	100	30 (7–114)	100	44 (12–128)	16	- (<6–22)	Czech Rep., 2010
Raab et al., 2013	302	100	50 (20–260)	2	<80 (<80–290)	2	<10 (<10 – 30)	Germany, 2007–09
Antignac et al., 2013	48	90	79 (<5–330)	98	75 (<5–224)	100	50 (40–66)	France, 2007
Völkel et al., 2008	57	100	120 (28–309)	11	<200 (<200–290)	–	–	Germany, 2006
Bernsmann and Fürst, 2008	203	55	56 (<40–284)	56	90 (<80–610)	1	[b]	Germany, 2006
North America								
Zheng et al., 2021	50	100	30 (6.4–187)	86	14 (<16–51)	90	6.7 (<6.1–17)	USA, 2019
Tao et al., 2008	45	96	106 (<32–617)	89	36 (<30–161)	51	12 (<12–64)	USA, 2007
Asia								
Awad et al., 2020	10[e]	100	65[d] (16–177)	96	139[d] (64–308)	65	8[d] (<4–18)	China, 2016
Kang et al., 2016	264	99	50 (31–77)[f]	99	72 (52–110)[f]		–	Korea, 2013
Lee et al., 2018	293	100	48 (15–380)	88	40 (<10–657)	35	<10 (<10 – 133)	Korea, 2011
Fujii et al., 2012	30	–	–	93	89 (<40–194)	–	–	Japan, 2010
Liu et al., 2011	50	100	42 (9–198)	100	121 (25–1440)	–	–	China, 2009
Liu et al., 2010	1237	100	49 (6–137)	88	35 (<1–814)	–	–	China, 2007

LOQ: limit of quantification.
[a] Pooled samples.
[b] Only two samples >LOQ (180 and 160 ng/l).
[c] Geometric mean.
[d] Arithmetic mean.
[e] Subgroup living in Shanghai.
[f] Interquartile range.

Table A4.3. Summary of data from studies of PFAS concentrations (ng/L) in breast milk, taken from Fromme et al. (2022). Full citations for studies listed are found in Fromme et al. (2022).

Most of the studies reviewed by DWQI (2017a, 2018), Fromme et al. (2022), and LaKind et al. (2022) are from the general population not known to be impacted by PFAS-contaminated drinking water. In these studies in which maternal exposure was presumably from sources other than drinking water such as food and consumer products, PFOA and PFOS were frequently detected in breast milk at concentrations higher than the New Jersey MCLs of 14 ng/L and 13 ng/L, respectively.

PFAS data from breast milk samples that were recently collected from U.S. general population are most relevant to the Health Effects Subcommittee's current evaluation because U.S. general population exposures to PFOA and PFOS (as indicated by serum levels) have decreased substantially between 1999 to 2017-18 in NHANES monitoring (CDC, 2022). For this reason, the data from Zheng et al. (2021), a study of PFAS in breast milk collected from 50 primiparous women in the Seattle area in 2019, are of particular interest. Median, 75th percentile, and maximum concentrations for were 13.9, 25.3, and 50.7 ng/L for PFOA, respectively, and they were 30.4 ng/L, 63.0 ng/L, and 187 ng/L, respectively, for PFOS. The residences of 32 of the 50 subjects in Zheng et al. (2021) are at locations that receive city of Seattle Public Utilities (SPU) water system (Erika Schreder, personal communication); information on the source of drinking water at the residences of the other subjects was not identified. The SPU water system has monitored for PFAS since 2015 and has not detected PFOA or PFOS in any water sources that have been used since 2015 (Seattle Public Utilities, undated). Levels of PFOA and PFOS in breast milk from the subjects who used SPU water at home, presumed to not be exposed through drinking water or other point sources, were similar to levels for the overall study group, with median and maximum values for PFOA of 12.7 and 50.7 ng/L (the highest level in the study), respectively, and for PFOS, 30.4 and 89.8 ng/L, respectively (Erika Schreder, personal communication).

Additionally, LaKind et al. (2022) estimated concentrations of PFOA and PFOS in breast milk in the U.S. general population from the most recent (2017-18) NHANES serum data for women of childbearing age, using serum:breast milk transfer factors determined by averaging four values from the scientific literature. They estimated that the geometric mean and 95th percentile breast milk concentrations in the U.S. general population as 64.4 and 183.1 ng/L, respectively, for PFOA and 23.2 and 68.9 ng/L, respectively, for PFOS.

The data from Zheng et al. (2021) and LaKind et al. (2022) summarized above indicate that median PFOA and PFOS levels in breast milk from the U.S. general population are very close to or above the New Jersey Health-based of 14 ng/L for PFOA and 13 ng/L for PFOS. These levels of PFOA and PFOS in breast milk presumably result from maternal exposures to non-point sources of PFOA and PFOS, such as food and consumer products, with minimal or no impact from contaminated drinking water.

Concentrations of PFOA and PFOS in breast milk are much higher in women who consume drinking water contaminated with PFOA and/or PFOS. For example, as reviewed by DWQI (2017a), "breast milk concentrations [of PFOA] were much higher in … samples from Shanghai

province (urban mean, 616 ng/L; rural mean, 814 ng/L) than in 12 other Chinese provinces (mean, 46 ng/L). Maternal exposures were likely higher in Shanghai … because PFOA levels are higher in Shanghai drinking water and surface water, likely because many fluorochemical manufacturing plants are located there (Liu et al., 2010)." Additionally, Fromme et al. (2022) reported on PFOA concentrations in breast milk from an area in Bavaria with contaminated drinking water where serum PFOA levels are known to be elevated. Breast milk concentrations in this contaminated location were much higher (mean: 199 ng/L, range: 33-854 ng/L) than in the general Bavarian population (mean: 27 ng/L, range: <25 – 326 ng/L). Finally, LaKind et al. (2022) predicted highly elevated breast milk concentrations (geometric means of up to 2747 ng/L for PFOA and 551 ng/L for PFOS) at locations with contaminated drinking water throughout the U.S. These predictions were based on serum PFOA and PFOS data from these locations and the serum:breast milk transfer factors mentioned above.

In summary, the data reviewed above show that levels of PFOA and PFOS in breast milk at levels are above the New Jersey Health-based MCLs even in the absence of contaminated drinking water. Furthermore, concentrations of these PFAS in breast milk are much higher when drinking water is contaminated. These data indicate that exposure to PFOA and PFOS in drinking water should be minimized, partcularly because infants are a susceptible subpopulation for effects of these PFAS. This information further supports the conclusion that Health-based MCLs for PFOA and PFOS should be below the NJ PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS.

APPENDIX 5. CONSIDERATION OF RISKS OF PFAS MIXTURES

Potential toxicological interactions of multiple PFAS that co-occur in drinking water are relevant to the discussion of whether current scientific information supports Health-based MCLs below the current New Jersey PQLs of 6 ng/L for PFOA and 4 ng/L for PFOS. A draft USEPA document on potential approaches for the evaluation of risks of PFAS mixtures (USEPA, 2021c) was developed as part of USEPA's overall effort to regulate PFOA and PFOS in drinking water and was reviewed by USEPA SAB (2022). In addition, at least four states (Maine, Massachusetts, Oregon, Vermont) have established drinking water guidelines based on the total concentration of multiple (four to six) PFAS (ITRC 2022a), and at least one other state (Minnesota) assumes dose additivity for contaminants (including PFAS and others) that cause the same general toxicological effect (MDH, 2020). The European Union and some European nations have also developed drinking water guidelines for mixtures of PFAS (ITRC,2022a). When PFAS co-occur, consideration of toxicological interaction of mixtures decreases the maximum allowable levels of any one compound.

Overview of potential approaches for assessing risks of PFAS mixtures

Experimental data on the toxicity of defined PFAS mixtures is extremely limited, particularly from mammalian species. A review of the literature through 2020 (ITRC, 2022b; Section 17.2.7.2) identified six studies of receptor activation or toxicity in cultured cells and two toxicity studies in zebrafish; no *in vivo* toxicity studies in mammalian species were identified. A more recent review by USEPA (2021c) identified three mammalian toxicity studies and one additional study in cultured cells, all of which were published in 2021. More recently, a study of maternal and offspring effects of combined exposure to PFOA and PFOS in rats conducted by the USEPA Office of Research and Development (Conley et al., 2022) was published in November 2022 and is discussed in detail below.

Proposed approaches for addressing risks of PFAS mixtures are reviewed in ITRC (2022b, Section 17.2.7.1) and USEPA (2021c). These include the total concentration (simple additive) approach, the Hazard Index approach, and the Relative Potency Factor approach.

In the total concentration (simple additive) approach, it is assumed that all of the PFAS that are included are equally potent and cause the same toxic effects, and that their toxicity is additive. The drinking water guideline is based on the total concentration of a specific group of PFAS (e.g., certain long-chain PFAS). Although this approach is not strictly science-based, since the toxicological potencies and most sensitive toxicological effects clearly differ among PFAS, it has been applied as a conservative public health-protective policy decision by some states and internationally. For example, the Vermont, Massachusetts, and Maine drinking water guidelines for PFAS MCL of 20 ng/L apply to the total concentration of five or six long-chain PFAS (PFOA, PFOS, PFNA, PFHxS, and PFHpA in VT; also includes PFDA in MA and ME), while the Oregon guideline of 30 ng/L applies to the total of four PFAS (PFOA, PFOS, PFNA, PFHxS (ITRC, 2022a). Although there are virtually no toxicity data for PFHpA and its human half-life is shorter than PFOA's, a science-policy decision was made by Vermont, Maine and Massachusetts to assume that PFHpA is equally toxic as the other longer chain PFAS.

The Hazard Index approach, originally developed by USEPA (1989), is based on the assumption of dose additivity for non-cancer effects, and it is often used to evaluate potential risks at contaminated sites. In this approach, the Hazard Quotients (fractions of the RfDs or similar non-cancer toxicity factors such as ATSDR Minimal Risk Levels) for individual chemicals (which may include both PFAS and other contaminants) are added to determine a Hazard Index. The Hazard Index can be based on chemicals whose toxicity factors are based on different toxicological endpoints as an initial screening approach, or chemicals whose toxicity factors are based on the same toxicological endpoint as a more definitive approach (ATSDR, 2020; USEPA, 2021c). A Hazard Index of < 1 indicates that adverse effects are unlikely, while a Hazard Index of ≥ 1 is interpreted as suggesting potential risks that warrant further investigation and/or actions to reduce exposure. The Minnesota Department of Health (MDH, 2020) uses an approach analogous to a Hazard Index (called a Health Risk Index) to evaluate risks of contaminants that co-occur in groundwater. It is based on grouping contaminants (including PFAS and others) that cause toxicity to the same target organ (e.g., liver, kidney, thyroid).

The Relative Potency Factor (RPF) approach is also based on the assumption of dose additivity. An RPF is assigned to each PFAS based on its relative potency for a common toxicological effect as compared to an index compound (for example, PFOA) which is assigned a potency factor of 1. To assess the risks of a PFAS mixture, the concentration of each PFAS that is present in the environmental medium of interest (e.g., drinking water) is multiplied by its RPF. The RPF-adjusted concentrations are then summed, and the toxicity of the total RPF-adjusted concentration is assumed to be equal to the equivalent concentration of the index compound.

The RPF approach (also known as the toxicity equivalency factor [TEF] approach) has been used for evaluation of the risks of several groups of chemicals known to act through a common and well-defined mode of action (MOA), including cholinesterase-inhibiting pesticides (organophosphates) and polychlorinated dibenzo-para-dioxins and dioxin-like compounds (polychlorinated dibenzofurans; dioxin-like PCBs) whose MOA is activation of the AhR receptor. However, use of the RPF approach for PFAS is more uncertain, because, as discussed by the NJDEP Science Advisory Board (NJDEP SAB, 2019), the toxicological effects of PFAS do not occur through a single common MOA, such as activation of a specific receptor. Furthermore, the MOA may not be the same for all toxicological effects of a specific PFAS or for the same toxicological effect caused by different PFAS.

RPFs for 22 PFAS, with PFOA as the index compound, were proposed by Bil et al. (2021). This publication is an extension of an RPF approach for 18 PFAS developed by RIVM (Netherlands National Institute for Public Health and the Environment) scientists (RIVM, 2018). RPFs were based on increased relative liver weight, without the requirement that this effect occurs through a common MOA, from studies of PFOA and 15 other PFAS with durations of 40-98 days because data were available for more PFAS for this endpoint than for other hepatic effects (e.g., absolute liver weight, hepatocellular hypertrophy). Relative liver weight data (based on external doses) were fit to parallel dose-response curves that were determined to provide an acceptable fit to the data, and a BMD_{05} was developed for each PFAS. RPFs ranging from 0.001 (PFBS) to 10 (PFNA) were developed from the ratio of the BMDs for each PFAS to the BMD for PFOA. RPF

ranges for seven additional PFAS for which no relative liver weight data were available were estimated by read-across/interpolation.

It is noted that the RPFs proposed by Bil et al. (2021) may not be sufficiently protective. As discussed by NJDEP SAB (2019), although increased relative liver weight was observed for all PFAS that were evaluated for this effect, "…other effects are more sensitive for specific PFAS including delayed mammary gland development for PFOA (DWQI, 2017a) [and] immune system suppression for PFOS (DWQI, 2018)." NJDEP SAB (2019) also noted that the RPF approach "is only applicable to compounds for which the relative potency for the effect used for the RPFs is known… or can be estimated from closely related compounds. Therefore, … this approach is not applicable to mixtures that include …. PFAS that lack known or estimated toxicity data for the target effect."

Finally, NJDEP SAB (2019) noted that "the … RPFs developed by RIVM (2018) are based on the external (administered) doses to the male rats …[and] do not account for differences in the relative half-lives between humans and male rats (i.e. differences in the human:male rat half-life ratio). Based on the half-lives presented in RIVM (2018), the human:male rat half-life ratios range between 8 for PFBA and ~500 for PFOA, and consideration of these differences would substantially affect some of the RPF values."

Bil et al. (2022) extended the earlier work of Bil et al. (2021) to develop RPFs for 10 PFAS based on serum levels rather than external doses. They used toxicokinetic models to estimate blood serum PFAS levels at which hepatic effects occurred in male rats. However, these blood serum-RPFs are intended for evaluation of the risks of mixtures of PFAS detected in serum in human biomonitoring studies and are not intended for assessment of risk of PFAS mixtures in drinking water. Additionally, they do not account for the differences in relative half-lives between humans and male rats mentioned above.

Conley et al. (2022) study of effects of co-exposure to PFOA and PFOS during gestation in rats

A recent study from the USEPA Office of Research and Development toxicology laboratories (Conley et al., 2022) evaluated maternal and offspring effects in dams dosed on gestation day (GD) 8 through postnatal day (PND) 2 with PFOA (0, 10, 30, 62.5, 125 mg/kg/day; n=5 per group), PFOS (0.1, 0.3, 1, 2, 5 mg/kg/day; n=5 per group), or a mixture of PFOS (2 mg/kg/day) and PFOA (0, 3, 10, 30, 40, 62.5, 80 mg/kg/day) (n=5 per group - 0 and 5 mg/kg/day; n=4 per group – 2, 10, 30, 40, 62.5 mg/kg/day). Blood and liver were collected from two pups from each litter sacrificed at delivery; one liver underwent histopathological examination and the other was used for glycogen measurement. All dams and the remaining pups were sacrificed on PND2. Maternal endpoints evaluated were serum and liver PFOA and PFOS concentrations; body weight on GD8, GD22, and PND2; body weight gain from GD8-GD22; number of uterine implants, absolute and relative liver and kidney weights and histopathology; free triiodothyronine (T3), and total T3 and thyroxine (T4); clinical chemistry. Offspring endpoints included serum and liver PFOA and PFOS concentrations; litter size; pup birthweight (absolute and adjusted for delivery time and litter size); percent of implants and percent of pups born alive surviving until PND2; absolute and relative liver weight on PND2 (one per sex per litter); liver

histopathology (pups sacrificed at delivery and all PND2 pups); total T3 and T4, and reverse T3; and clinical chemistry (pooled blood from each litter).

Concentrations of PFOA and PFOS in serum and liver from the same administered dose were not significantly different from co-exposure as compared to exposure to the individual compounds. Co-exposure to PFOS (2 mg/kg/day) shifted the dose-response curve for PFOA for many maternal and pup endpoints such that the effects of a given dose of PFOA was greater than without co-exposure to PFOS. Offspring endpoints for which such a shift in the PFOA dose-response curve was observed included survival (both as percent of implants and percent born alive), body weight gain, relative liver weight, total T3, creatine, globulin, glucose bile acids, total bilirubin, blood urea nitrogen, and total protein. Maternal endpoints for which a shift to a greater effect in the PFOA dose-response curve occurred included absolute and relative liver weight, blood urea nitrogen, total protein, globulin, and glutamate dehydrogenase (GLDH). In contrast, the PFOA dose-response curves for maternal body weight on GD22 and weight gain on GD8-GD22, and offspring serum triglycerides, were shifted to a smaller effect at a given dose with co-exposure to PFOS. For other endpoints including birthweight, liver glycogen, cholesterol, GLDH, and aspartate aminotransferase in offspring and body weight on PND2, weight gain on GD8-PND2, triglycerides, and ALT in dams, co-exposure to PFOS did not significantly affect the PFOA dose response curve, and data for some other endpoints (e.g., liver histopathology) was not amenable to this type of analysis.

Endpoints with dose-response curves amenable to dose additivity and response additivity modeling predictions included offspring survival to PND2 (percent of uterine implants and percent of those born alive), offspring bodyweight on PND1 and PND2, offspring total T3 and liver glycogen, and maternal weight gain (GD8-GD22) and relative liver weight. Dose additivity adequately described the interaction of PFOA and PFOS for all endpoints except maternal weight gain, while response additivity adequately described only offspring body weight on PND 1 and PND2. Relative potency factors for PFOS, with PFOA as the index compound assigned a value of 1, varied widely for both maternal endpoints (7.8-26.3) and pup endpoints (1.8-43.7). The authors concluded that their results "support the hypothesis of cumulative effects on shared endpoints from PFOA and PFOS co-exposure and dose additive approaches for predictive estimates of mixture effects."

Previous Health Effects Subcommittee conclusions about risks of PFAS mixtures

Health-based MCLs developed by the Health Effects Subcommittee (DWQI, 2015, 2017a, 2018) for PFNA, PFOA, and PFOS were based on consideration of health risks of each compound individually. A primary reason for the decision not to consider toxicological interactions of PFAS mixtures when developing the Health-based MCLs was the desire for consistency with the approach used for Health-based MCLs for other contaminants that were previously developed by the Subcommittee. Although toxicological interactions were not considered quantitatively, the Subcommittee acknowledged the potential for additive toxicity of PFAS that co-occur in drinking water as an uncertainty in its assessments, as follows:

For PFNA (DWQI, 2015): “Available information indicates that the target organs and modes of action are generally similar for PFNA and other PFCs, particularly PFOA. Therefore, the toxicity of PFNA and other PFCs may be additive. Although PFNA and other PFCs, including PFOA, are known to co-occur in some NJ public water supplies, the potential for additive toxicity of PFNA and other PFCs was not considered in development of the Health-based MCL.”

For PFOA (DWQI, 2017a): “Available information indicates that the target organs and modes of action are generally similar for PFOA and some other PFCs, including PFNA (DWQI, 2015). Therefore, the toxicity of PFOA and other PFCs may be additive. Although PFOA and other PFCs, including PFNA, are known to co-occur in some NJ public water supplies, the potential for additive toxicity of PFOA and other PFCs was not considered in development of the Health-based MCL.”

For PFOS (DWQI, 2018): “Available information indicates that the toxicological effects are generally similar for PFOS and some other PFCs, including PFOA (DWQI, 2017a). Additionally, the health effects associated with PFOS in epidemiology studies are also associated with PFOA. Therefore, the toxicity of PFOS and other PFCs may be additive. Although PFOS and other PFCs, including PFOA, are known to co-occur in some NJ public water supplies, the potential for additive toxicity of PFOS and other PFCs was not considered in development of the Health-based MCL.”

USEPA (2021c) recommendations for assessing risks of PFAS mixtures and USEPA SAB (2022) review

As part of USEPA’s overall effort to develop National Primary Drinking Water Standards (MCLs or a Treatment Technique) for PFOA and PFOS, a draft framework for assessment of risks of non-carcinogenic effects of PFAS mixtures (USEPA, 2021c) was developed and reviewed by USEPA SAB (2022).

USEPA (2021c) reviewed several types of information indicating the need for approaches for evaluating PFAS mixtures in the environmental. This included occurrence data demonstrating that PFAS commonly co-occur in drinking water and other environmental media, biomonitoring data indicating that humans are exposed to multiple PFAS, and toxicology data showing that many PFAS cause common toxicological effects such as hepatic, developmental, and immune system toxicity.

The draft framework proposed by USEPA (2021c) includes component-based approaches based on the assumption of dose additivity. It supported the assumption of dose additivity by reviewing data indicating that toxicological interactions are almost always additive or close to additive, and that assuming dose additivity usually does not underestimate toxicity of a mixture. A tiered approach that includes use of a Hazard Index (screening approach based on assumed dose additivity for PFAS regardless of whether they cause common toxicity), a Target Organ Specific Hazard Index (assumed dose additivity for PFAS with common target organ toxicity), and RPFs (as described above) was recommended.

USEPA (2021c) proposed that the RPF approach for PFAS be based on a common toxicological effect and that knowledge of the MOA and/or identification of a common MOA are not required. To support this recommendation, USEPA (2021c) noted that "… PFAS are an emerging chemical class of concern, MOA data are limited or not available for many PFAS," and cites USEPA (2000) RPF guidance that states: "The common mode-of-action assumption can be met using a surrogate of toxicological similarity, but for specific conditions (endpoint, route, duration)."

USEPA SAB (2022) supported the USEPA (2021c) assumption of dose additivity based on a common health outcome (e.g., toxicological effect) as a health protective default approach for assessment of risks of PFAS mixtures. They agreed with USEPA (2021c) that identification of a common MOA is not required. That being said, the SAB recommended that "the uncertainties associated with … [assumed dose additivity] be more thoroughly and clearly presented along with information supporting this approach," and also recommended that "when data clearly indicate interactions other than dose additivity, the approach indicated by the data should be used," and that USEPA should "reevaluate the default assumption of dose additivity as additional data become available." Additionally, SAB (2022) noted that studies supporting a common MOA and dose additivity for PFAS are discussed in the draft document (USEPA, 2021c) and recommended that studies that "do not indicate dose additivity and/or a common MOA" also be included. USEPA SAB (2022) also noted that the examples presented in USEPA (2021c) are based on PFAS with toxicity factors based on animal data. Since the draft USEPA PFOA and PFOS RfDs are based on human data, USEPA SAB (2022) recommended that approaches for mixtures of PFAS with toxicity factors based on human data, and for mixtures of PFAS with some toxicity factors based on animal data and others based on human data, be developed by USEPA.

Conclusions for consideration of risks of mixtures of PFAS in drinking water

The information reviewed above supports consideration of toxicological interactions of PFAS that co-occur in drinking water. The focus of the evaluation presented herein is whether Health-based MCLs for PFOA and PFOS below the current NJ PQLs are supported by current scientific information, and the scope of this evaluation does not include recommendation of a specific approach for consideration of risks of PFAS mixtures. That being said, recognition that the toxicological effects of PFOA, PFOS, and/or other PFAS that co-occur in drinking water are likely to be additive or synergistic (greater than additive) supports more stringent Health-based MCLs than if such interactions were not considered. Therefore, the information discussed above provides additional support for revision of the NJ Health-based MCLs for PFOA and PFOS to more stringent values.

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