Maximum Contaminant Level Goal Drinking Water Recommendations for Per- and Polyfluoroalkyl Substances (PFAS) in the Commonwealth of Pennsylvania

By
The Drexel PFAS Advisory Group

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1. Executive Summary

The Drexel PFS Advisory Group (DPAG) is a unique multidisciplinary team engaged by the Commonwealth of PA to provide recommendations for Maximum Allowable Contaminant Level Goals MCLGs to the Commonwealth of Pennsylvania for Per- and polyfluoroalkyl substances (PFAS) in drinking water. Observational epidemiology supports the need for drinking water values below the current recommendations of the United States Environmental Protection Agency (US EPA) lifetime health advisory LHA level of 70 ppt for PFOS and PFOA individually or in combination. Furthermore, the identification of other PFAS in drinking water requires a broader consensus consideration of all these substances. As of this report, the US EPA has not initiated its process for establishing MCLs or MCLGs under the Safe Drinking Water Act. Therefore, specific guidelines for the Commonwealth of Pennsylvania were deemed necessary to protect the safety and well-being of Pennsylvanians.

The DAPG consist of experts in the fields of medical toxicology, epidemiology, environmental toxicology, water drinking standards, and risk assessment. The biographies of the members of the DPAG are included as Appendix A.

The Pennsylvania Department of Environmental Protection (PADEP) tasked the DPAG to review the existing and proposed PFA standards from across the country and independently develop MCLGs to inform the initial phase of the rulemaking process for establishing state drinking water standards. (Appendix B and C) The effort commenced in January 2020 and continued to the delivery of this report. Because of restrictions on

face-to-face interactions due to the Covid19 pandemic, much of the advisory groups work was done through virtual conferences between DPAG and PA DEP during 2020.

The DPAG methodically evaluated existing and proposed standards from across the country for PFAs considered under US EPA method 537.1. PADEP asked DPAG to provide specific recommendations on perfluorononanoic acid (PFNA), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluoroheptanoic acid (PFHpA), and perfluorobutanesulfonic acid (PFBS). DPAG added the ammonium salt of hexafluoropropylene oxide dimer (GenX) to the list of reviewed PFAS. This latter addition was approved by the PA DEP.

PA DEP charged the advisory group with producing MCLGs within a year. Hence, the initial effort was to review the existing national and state derive PFA assessments, review the pertinent literature in a focused manner, and generally benefit from prior efforts to develop PFAS health-based values. Once complete, the DPAG independently reconsidered all of the PFAS in question and formed draft recommendations for the PA DEP in the summer of 2020.

The PA DEP placed no expectations on the DPAG other than a scientifically defensible approach in developing these values.

Furthermore, by charging a group with developing MCLGs, the commonwealth asked that we focus on developing values that were not as much influenced by technical difficulties necessary to achieve them – e.g. measurement, remediation, or other mitigation. DPAG purposely sought to maintain an independent mindset with developing these MCLGs and to focus on identifying concentrations that would protect

human health. Each consideration and the evidence behind the evaluation as well as methodical calculation are included in the individual summaries. The Reference Dose and recommended Chronic Non-Cancer MCLGs for the seven PFAS considered are Table 1.

PFAS	Reference Dose	MCLG proposed
perfluorooctanoic acid (PFOA)	3.9 ng/kg/day	8 PPT
perfluorooctanesulfonic acid (PFOS)	3.1 ng/kg/day	14 PPT
perfluorononanoic acid (PFNA)	2.2 ng/kg/day	6 PPT
perfluorohexanesulfonic acid (PFHxS)	4.0 ng/kg/day	20 PPT
perfluoroheptanoic acid (PFHpA)	None derived	8 PPT
perfluorobutanesulfonic acid (PFBS)	39 ng/kg/day	55 PPT
ammonium salt of hexafluoropropylene oxide dimer (GenX)	75 ng/kg/day	108 PPT

Table 1: Summary of Reference Dose and proposed Chronic Non-Cancer MCLG for perfluorononanoic acid (PFNA), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluoroheptanoic acid (PFHpA), perfluorobutanesulfonic acid (PFBS), and the ammonium salt of hexafluoropropylene oxide dimer (GenX)

2. Background

Per- and polyfluoroalkyl substances (PFAS), and the polymers and surfactants made from them, are a large family of greater than 4000 man-made chemicals that contain carbon, fluorine, and other elements and have been used widely in many industrial and consumer applications since the 1950's. Perfluoroalkyl substances are aliphatic substances where all of the carbons are attached to fluorine with the exception of the last one. Polyfluoroalkyl substances are aliphatic substances where at least one, but not all of the carbons are attached to fluorine and contain the perfluoroalkyl moiety (C_nF_{2n+1}).

The carbon-fluorine bond is stable and strong. The perfluoroalkyl moiety's chemical and thermal stability as well as its lipophobic and hydrophobic properties allow it to be very useful in a variety of industries world-wide. They are used to help make products more resistant to oils, grease, stains, and water, and they are used in many industries because they help reduce friction, through their surfactant applications by lowering their surface tension properties i.e. automotive, construction, aerospace. These properties also contribute to their bioaccumulation and environmental persistence. The length of the fluorinated carbon chain distinguishes the short from the long chain PFAS. Long chain PFAS are perfluoroalkyl carboxylic acids with 8 or more carbon chains and perfloroalkane sulfonic acids with 6 carbon chains and greater. While not specifically stated, perfluoroalkyl chains with 7 or greater carbon atoms are generally considered long chain. The fluorinated carbon chain length determines properties that influence the substance behavior in the environment, organisms, and bioaccumulation. Long chain

compounds include PFNA (9 carbon carboxylic acid), PFOA (8 carbon carboxylic acid), PFHpA (7 carbon carboxylic acid), PFOS (8 carbon sulfonic acid), and PFHxS (7 carbon sulfonic acid). Short chain PFAS include GenX chemicals (6 carbon oxide dimer acid), and PFBS (4 carbon sulfonic acid).

PFASs are present in the environment as a result of their use in a wide array of industrial, commercial, and residential products and applications, including newspaper printing, textile and paper production, metal plating, surfactants in fluoropolymer production, and aqueous film-forming foams (AFFFs), and include consumer products such as outdoor apparel, dental floss, and car wax (Prevedouros 2006, Paul 2008, Konwick 2008). PFASs are emitted to the environment both directly throughout their product and use cycle and indirectly from transformations of their precursors. The majority of emissions are released directly into aquatic environments (Prevedouros 2006, Paul 2008); however, accurate quantification of emissions and resulting environmental exposure are largely lacking (Guo 2009).

2.a. PFAS in Wastewater

PFAS have been found in wastewater treatment plant influents from both municipal and industrial sources, with treated wastewater effluents and sewage sludges (including biosolids) now being viewed as major sources of PFAS to the aquatic environment (Ahrens 2011), which may substantially impact rural water sources. A range of poly- and perfluoroalkyl acids (PFAA) have been routinely detected in wastewater effluents in various countries, including the United States (US) (see review by Hamid 2016). In addition to treated wastewater, various PFAS compounds have been detected in sewage sludges (Venkatesan 2013). In fact, a review by Clarke (2011) ranked PFAS as

the highest priority group of emerging contaminants in biosolids. Taken together, due to the unmitigated use of PFAS in consumer products and the long-term persistence of these compounds, reuse of treated wastewater or land application of biosolids may present a source of PFAS that impact rural communities and agricultural operations.

2.b. PFAS from Landfill Leachate

Due to the widespread use of PFAS in commercial products, various congeners and concentrations of PFAS are likely to be present in all landfills. Landfills receiving waste from industrial facilities (e.g., paints, textiles used in furniture, carpet, upholstery) are expected to have higher concertation of PFAS (Guerra 2014, ITRC 2020). However, low concentrations of PFAS have been detected in the range of ppt to ppb levels at municipal landfills likely due to the use of PFAS on some paper products (Arvaniti 2012, Renou 2008, ITRC 2020). It is important to note that some landfills transferred their leachate to WWTPs for treatment. Perfluoroalkyl sulfonic acids (PFSAs) and Perfluoroalkyl carboxylic acids (PFCAs) are the most common PFASs in landfills, which are known as PFAAs. PFCAs and PFSAs have the carbon chain length C4-C18 as well as C4-C10, respectively. Additionally, PFAAs precursors (e.g., FTOH, n:2 FTCA, and n:2 FTUCAs) existing in the consumer products (Ye 2015; Kotthoff 2015) can degrade to PFAAs throughout disposal in the landfill and product use (Lang 2016, Allred 2015).

2.c. PFAS from the use of AFFF

The U.S. Department of Defense (DoD) has used aqueous film forming foam (AFFF) to suppress fires since the 1970s. PFASs are known to contaminate over 500 DoD sites (Thompson 2012), and repeated historic use at firefighter training areas has

resulted in groundwater and porous media contamination, with groundwater concentrations of select PFASs reaching low mg/L levels (Moody 1999, 2000, 2003, Anderson 2016, Murray 2010, Backe 2013, McGuire 2014, Filipovic 2015, Schultz 2004). While PFAAs are often not the dominant PFASs in AFFF formulations at impacted sites, PFAAs and 6:2 FtS are often the dominant PFASs found in contaminated groundwater (Backe 2013, Houtz 2013, McGuire 2014, Schultz 2004). The predominance of PFAAs in groundwaters is hypothesized to be a result of abiotic and biotic reactions in the subsurface that transform the parent PFAS compounds in AFFF formulation (*e.g.*, fluorotelomer thioamido sulfonates, FtTAoS) into FtSs and PFAAs (Harding-Marjanovic 2015).

2.d. PFAS Fate and Transport in the Environment

While there are many aspects that make PFASs chemistry unique, of particular note are their biological and chemical stability, promoting their persistence in the environment), and the comparatively high solubility limits and adsorptive nature of some PFASs, especially of shorter chain length, making them relatively mobile in aqueous systems (Zareitalabad 2013). Perfluoroalkyl acids (PFAAs), which have a negatively charged head group, low volatility, and high water solubility, are considered to be highly mobile in aqueous phases (Ahrens 2011, Ahrens and Bundschuh 2014), and PFAA transport has often been observed or inferred in the environment (Moody 1999, Lindstrom 2011, McGuire 2014, Baduel 2015, Filipovic 2015). As a consequence of such mobility and concerns of their human health effects, drinking water wells at several downstream localities of DoD sites have been temporarily abandoned. The sorption behavior of PFASs is influenced by their physicochemical properties which vary

depending on their functional head group and chain length (Ahrens 2009, 2011, Ahrens and Ebinghaus 2010). PFAA sorption generally increases with increasing chain length. Longer chain length PFAAs have been demonstrated to bioaccumulate and possibly biomagnify. (Prevedouros 2006, Conder 2008) In addition to the ecological effects, bioaccumulation within a food web may lead to human exposure through dietary consumption (e.g., fish). As a consequence, sediments and biota are considered to act as a sink for longer chains PFAAs in aquatic ecosystems.

3. Approach

The DPAG reviewed a number of recommendations made by EPA and State agencies that chose to create a summative approach to PFAS, combining multiple minimal risk levels or advisory levels into one cumulative drinking water value. No clear consensus exists on this approach and the use of a summative approach was clearly designed to be a shortcut based on a presumption that the agents all have similar health effects and endpoints. While this approach may work for other toxins such as dioxins, furans, and coplanar polychlorinated biphenyls, it does not appear to be based on evidence available for PFAS. The DPAG therefore committed early in the process to developing an individual MCLG for each of the requested PFAS. DPAG further recommends that all PFAS be reviewed individually as they arise for analysis, even if the individual MCLG ultimately needs to be based on chemical similarities to other PFAS only (e.g. see PFHpA in our recommendations).

For each of the PFAS studied, the DPAG identified points of departure and rationale for selection from risk assessments published by other states, the EPA, and a TSTR. DPAG then assessed the underlying critical studies driving the selection of the POD. Every effort was made to use the experience and published findings from other agencies and build and refine on these as much as possible into a best practice approach. USEPA (2000), Beck (2016)

3.a. Maximum Contaminant Level Goals

Maximum Contaminant Level Goals (MCLGs) are maximum drinking water concentrations designed to protect human health. MCLGs are non-enforceable as they are chosen solely based on protection of human health and do not take into account whether analytical testing is available to detect the contaminant at the MCLG level or whether adequate technology exists to remediate or remove the contaminant at the MCLG level. Conversely, Maximum Contaminant Levels (MCLs), are derived from MCLGs but also take into account the availability of analytical testing, adequate technology for contaminant remediation, efficacy under field conditions, and cost. MCLGs include a margin of safety incorporated into the level via the use of uncertainty factors that ensures no adverse human health effects would result from lifetime exposure to the contaminant in drinking water at the MCLG level. MCLGs are derived separately for and non-cancer endpoints and cancer endpoints.

3.b. Non-Cancer Endpoints

The derivation of an MCLG is based on the assumption that for non-cancer endpoints, a dose threshold exists. Doses above that threshold potentially place a

person at risk for an adverse human health effect, whereas below that threshold the person is not at risk. To ensure that exposure at the MCLG and below does not place any person, including vulnerable populations, at risk, an adequate margin of safety is built into the derivation.

Available animal model studies are reviewed to determine the point of departure (POD), which is the first step in the MCLG derivation. The point of departure (POD) may be an administered dose, a modeled dose, or a serum level. If the POD is a serum level, a dose adjustment factor may be applied to derive a dose. In considering animal model studies as candidates for the POD, a number of factors should be considered, study duration (acute, subacute, chronic), route of exposure, intensity of exposure, study quality, relevance of the animal model adverse health effect to human health, and interspecies differences in absorption, distribution, metabolism and excretion of the substance. Animal model studies may be considered irrelevant for the derivation of an MCLG based on the above considerations and therefore not be used for the POD.

If an animal model study meets the criteria discussed above and is considered relevant to human health, then it serves as a candidate along with other such studies for the POD. Several PODs are available. The most commonly used POD is the no-observed-adverse-effect level (NOAEL), the highest dose administered in the animal model study that did not result in toxicity where toxicity is defined by alteration of biomarkers, change in body weight or body weight gain, lesions, or anatomical abnormalities at necropsy. In some circumstances, such as the absence of a NOAEL in an animal model study, the lowest-observed adverse-effect level (LOAEL) may be used as the POD. (USEPA 2002)

An alternative POD that may be used with robust datasets is the lower confidence limit of the benchmark dose (BMDL). Calculating the BMDL requires sufficient datapoints from the animal model study/studies that a dose-response curve can be modeled. The benchmark response (BMR) is the acceptable level of change in the animal model adverse health effect. A BMR of 10% is typically considered the acceptable level of change as it is at or near the limit of sensitivity of many bioassays. For continuous variables (e.g. body weight), a BMR of 10% corresponds to a 10% deviation in the outcome of interest, whereas for quantal data (e.g. organ toxicity) a BMR of 10% corresponds to a 10% increase in the incidence of the adverse effect. Statistical modelling of the dose response curve is used to calculate the dose that corresponds to the chosen BMR, known as the benchmark dose (BMD), and the lower 95% one-sided (or two-sided) confidence limit of the BMD is the BMDL. The DPAG, in discussion with the PA DEP, determined that the BMDL that corresponded to a BMD with a BMR of 10% (referred to as the $BMDL_{10}$) would be the default POD when the BMD method was employed. (USEPA 2012)

The EPA recommends a number of approaches to derive human equivalent oral exposures (HED) from a laboratory animal species derived POD. (USEPA 2002) The preferred approach is physiologically-based toxicokinetic modeling applying a dose adjustment factor. The DAF is multiplied by the animal exposure (in mg/kg/d) to achieve the human equivalent exposure (in mg/kg/d). In lieu of data to support either of these types of approaches, body weight scaling to the 3⁄4 power (i.e., BW3/4) is endorsed as a general default procedure to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purposes of deriving

an oral Reference Dose (RfD). Use of these methods is generally combined with a default interspecies uncertainty factor, UFA, reduced from 10 to $10^{0.5}$.

Once the HED is identified, the reference dose (RfD) is calculated by dividing the HED by uncertainty factors (UF) to create an adequate margin of safety. UFs have a value between 10^0 (i.e. 1), $10^{0.5}$ (i.e. 3), or 10^1 (i.e. 10). A default UFH of 10 is applied for the potential variability in sensitivity to the exposure in the human population. An UFA of 10 each is applied for the uncertainty of extrapolation from an animal model to humans unless some dose adjustment factor can be accurately applied. A default UFL of 10 is applied when the LOAEL is used rather than the NOAEL or BMD. A UFS is applied when extrapolating from sub-chronic animal model studies to chronic human exposure. An additional UFD, referred to as a modifying factor, may be applied to account for uncertainty about the quality of the study or data set. All the UFS are multiplied to develop a UFT, or total uncertainty factor. Figure 1 provides an illustration but does not represent an actual PFA or the order of endpoints.

Point of Departure Determination

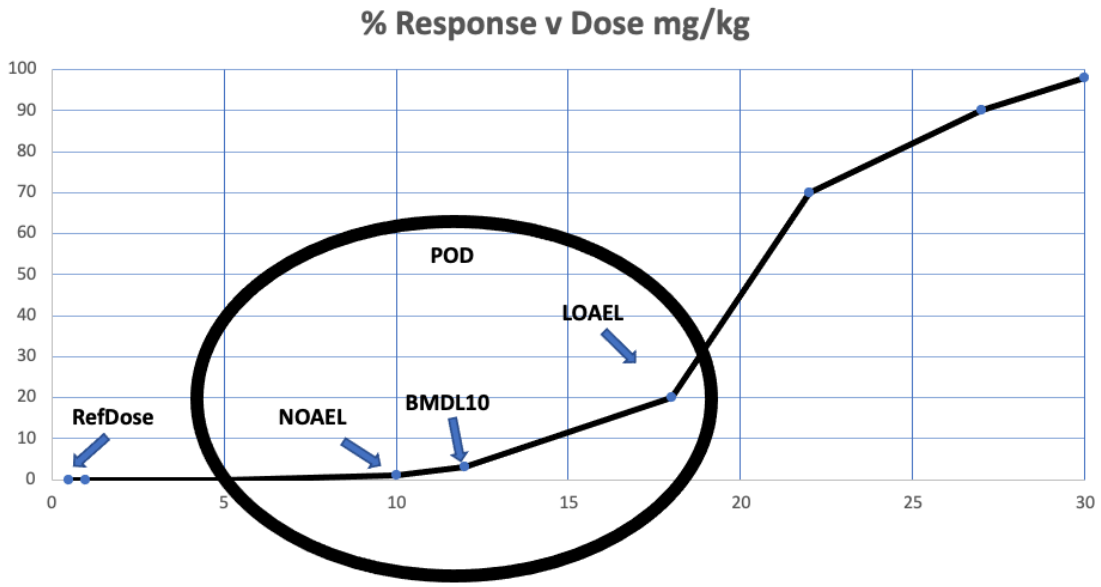

Figure 1: POD sought amongst various endpoints (LOAEL, NOAEL, $BMDL_{10}$) and then a Reference Dose derived.

The RfD is typically expressed in mg/kg/d and is the daily ingested dose of a substance that is considered to be without an increased risk of an adverse human health effect. The RfD can be converted into a Drinking Water Equivalent Level (DWEL), the concentration of the substance in water that would yield the RfD for the target population based on established drinking water rates. If the POD suggests that the target population is adults, then standard assumptions about weight (e.g. 70-kg adult) and consumption (2-L of water per day) are used. Different weight and consumption standards are applied if the POD suggest the target population is, for example, infants.

The MCLG is subsequently derived from the DWEL by accounting for the relative source contribution (RSC) of drinking water to total daily dose of the substance so that the total daily dose does not exceed the RfD. For substances where the relative source contribution is unknown, a default RSC of 0.2 is used. When the relative contribution of various sources to daily dose has been determined, the RSC of drinking water may be used instead of the default RSC but may be no greater than 0.8 to account for potential unknown exposure sources. (USEPA 2000)

3.c. Goeden Model discussion

An alternative method to convert RfD to MCLG is the transgenerational toxicokinetic model. This approach considers water consumption from conception to adulthood and adjusts for the fact that relative source contribution of water is higher early in life. It assumes that a child will have a certain level of exposure in-utero because of the PFA in the mother's body and further exposure during breastfeeding or bottle feeding. This model requires specific toxicokinetic information about the substance in question and cannot be applied to every substance. The model for this report was provided to the DPAG by Minnesota Department of Health (MDH) as an excel spreadsheet. Parameters for this model are listed in Appendix C. Although RfD was always calculated, the POD serum level was divided by UFT to determine a corresponding internal target human serum level (THSV). Working backward from the target human serum level, reduced by 50% to account for the RSC of an infant, an MCLG was derived from the model so that the highest serum level ever achieved from birth to adulthood never exceeded the reference dose. The model had sufficient data for application to MCLG recommendations for PFOA, PFOS, PFNA, and PFHxS. Table 2 lists some of the key

model parameters and the preferred tendency (central or upper) of the parameter. Please note: The THSV is useful for informing public health policy and interpreting population-based exposure potential. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

Model Parameter	Tendency of Parameter	PFOA	PFOS	PFHxS	PFNA
Half-Life, days	Central	840 [a]	1241 [b]	1935	1417 [c]
Placental Transfer Ratio	Central	0.87 [d]	40 [d]	0.70 [d]	0.69 [d]
Breastmilk Transfer Ratio	Central	0.052 [d]	0.017 [d]	0.014 [d]	0.032 [d]
Volume of Distribution (V_d), L/kg	Central	0.170 [e]	0.230 [e]	0.25 [f]	0.200 [d,g]
Relative Source Contribution (RSC), %	Central	50	50	50	50
Duration of Exclusive Breastfeeding, months	Upper	12	12	12	12
a) Bartell 2010; b) Li 2018; c) Zhang 2013; d) MDH 2020, 2019; e) Thompson 2010; f) Sundstrom 2012; Ali 2019 g) ATSDR 2018					

Table 2: Exposure Model Parameters used in transgenerational model (Goeden 2019) for derivation of proposed MCLG.

3.d. Cancer Endpoints

MCLGs for cancer endpoints are historically set at zero although there may be scenarios under which a non-zero MCLG is appropriate for a cancer endpoint. The rationale behind a zero MCLG for cancer endpoints is that historically extrapolation of cancer risk from high dose animal studies to low dose human exposures was performed using the linear no-threshold model. The absence of a threshold in this extrapolation

model results in some cancer risk being associated with any dose. Therefore, the only level goal that can be considered protective of human health is zero. (USEPA 2005)

Current carcinogen risk assessment allows for the consideration of threshold effects in extrapolation of cancer risk. A threshold effect may be present if cancer is only observed when an exposure meets a certain intensity or duration. However, the absence of cancer at low level exposures should not be assumed to constitute a threshold as low level exposures may be associated with cancer risk that is undetected due to studies that are underpowered to detect cancer at that exposure intensity. The mechanism by which the carcinogen increases cancer risk may inform whether a threshold effect is present. If the carcinogen induces cancer secondary to a toxic effect then the threshold is the dose at which the toxic effect occurs and doses below that threshold, after applying uncertainty factors, should be considered non-carcinogenic. MCLGs for carcinogens that act by a mutagenic mode of action are still set at zero as the linear-no threshold model is most appropriate for that mechanism.

Substances that are only carcinogenic above a certain exposure intensity or duration may have non-zero MCLGs utilizing the same derivation process as for non-cancer endpoints, discussed above. For such substances, the MCLG for the cancer endpoint and the MCLG for the non-cancer endpoint are both derived and the lower value of the two serves as the overall MCLG for the substance.

Numerous epidemiological studies of PFAS, especially PFOA and PFOS, have examined occupational and environmental exposures but have failed to detect consistent findings across studies. (Bonefeld-Jorgensen 2011, Chang ET 2014, Eriksen 2009, Hardell 2014, Innes 2014, Klaunig 2015, Yeung 2013). The International Agency

for Research on Cancer (IARC) has classified PFOA as “possibly carcinogenic to humans” (Group 2B), based on limited evidence in humans that it can cause testicular and kidney cancer, and limited evidence in lab animals. The EPA has not officially classified PFOA as to its carcinogenicity. EPA’s Scientific Advisory Board, based mainly from studies in lab animals, stated that PFOA shows “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.”

PFOA and PFOS show positive associations with cancers of the prostate, kidney, testis, and thyroid but with a) only small elevations in relative risk intervals (0.5 and 2.0 (with 95% confidence intervals including 1.0), b) evidence of negative associations as well, and c) inconsistencies across the studies. Furthermore, exposure response relationships do not follow the monotonic pattern of increasing dose causing increasing response. The strongest example is that associations found at lower environmental community studies are not supported by those found in the workplace where exposures are higher by one or two orders of magnitude. Furthermore, although animal studies support target organ as the liver, testis (Leydig cells), and pancreas (acinar cells), these are not the types of cancers identified by human studies. Some drinking water recommendations rely on an effect produced by expression of peroxisome proliferator-activated receptor-alpha (PPARalpha) which is specific to rodents. For example, CEPA (2019) and NJDEP (2017, 2018) have cancer minimal risk levels for PFOA and PFOS derived heavily from animal studies. After careful review, the DPAG concluded that cancer endpoints for PFAS that rely heavily on animal studies are not supported by the totality of human and animal evidence. Furthermore, there is insufficient evidence to argue that Non-Cancer MCLGs would not be protective of cancer risk.

4. PFOA

After a literature search and a review of the available evidence and recommendations from various agencies, the DPAG developed an MCLG recommendation for PFOA based on Non-Cancer endpoints. The agencies with the most relevant inputs were the US EPA, the ATSDR (ATSDR 2018), the MDH (MDH 2020 PFOA), NJDEP (NJDEP 2017), and MDHHS (MDHHS 2019). The US EPA selected Lau (2006) because it met their criteria for chronic exposure, multiple dose groups, use of a concurrent control, and with serum data amenable for modeling. (US EPA 2016) MDH used Lau (2006) as well and used the serum level estimated by US EPA. The ATSDR selected identical LOAELs from Onishchenko (2011) and Koskela (2016). Both studies had the same populations of laboratory animals and evaluated a single dosing group. These studies identified developmental effects (neurobehavioral and skeletal) as critical. The DPAG selected Koskela (2016) and Onishchenko (2011) as the critical studies. (ATSDR 2018, Appendix A, Table A8)

The serum concentration at the LOAEL of 0.3 mg/kg/d from Onishchenko (2011) and Koskela (2016) was below the modeled serum concentrations from two immunotoxicity studies evaluated by ATSDR (a sensitive effect seen in other PFAS). (Lau 2006) MDHHS also selected the critical studies by ATSDR as also being protective for immunotoxicity. (MDDHS 2019) The DPAG rejected the BMDL from Loveless (2006) used by NJDEP. Loveless (2006) was a 14-day exposure study in rats and mice, with liver weight changes being the critical effect identified. NJDEP (2017) Liver weight changes, in and of themselves, translate questionably as an adverse effect in humans

and the POD identified was higher than those when considering immunotoxicity. From Onishchenko and Koskela, the ATSDR estimated the POD average serum concentration in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh 2013) using animal species-, strain-, sex-specific parameters. This was adopted by the DPAG as the POD for PFOA.

4.a. Review of Critical Studies

Koskela (2016) investigated the administration of PFOA at a dose of 0.3 mg/kg/d administered orally mixed with food to pregnant C57BL/6/Bkl mice starting on GD1 to investigate developmental outcomes on long bone morphology and bone cell differentiation. Female offspring were sacrificed at the age of 13 or 17 months for examination.

Body weights of PFOA exposed offspring were higher than controls throughout the lifetime of the animals, reaching statistical significance at 13 and 17 months. Significant increases in the femur and tibial periosteal area and medullary area were seen at 17 months but not at 13 months in PFOA exposed offspring. Tibial mineral density was decreased in PFOA exposed offspring at both 13 and 17 months. Femur and tibial cortical area, trabecular parameters, and femur mineral density were unaffected by PFOA exposure. There was no significant effect of PFOA exposure on biomechanical properties of the femur or tibia. Concentration of PFOA in pooled tibias and femurs was significantly greater in exposed offspring at both 13 and 17 months.

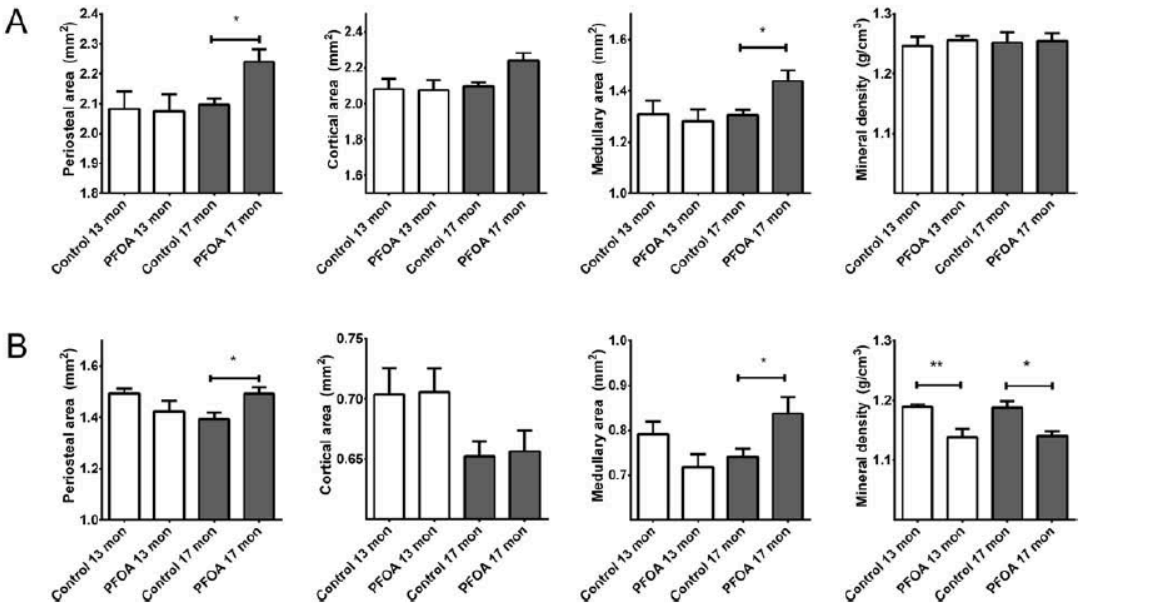

Fig. 2. Effects of PFOA on morphometrical parameters of femurs (A) and tibias (B) as analyzed by microCT. The cortical VOI reference point was set to the point where complete fusion of the growth plate was observed, offset being 250 and height 500 cross-sections proximally. Group mean ± SE, $n = 5$. $^{*}p < 0.05$, $^{**}p < 0.01$.

Figure 2: Effects of PFOA reproduced from (Koskela 2016). This represents the selected PFOA critical effect of morphometric parameters of femurs and tibias at 13 and 17 months - dosing is 0.3 mg/kg/d (LOAEL). The average serum concentration was estimated in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh 2013) using animal species, strain, sex-specific parameters. (ATSDR 2018)

In an in vitro study, the effect of PFOA on the viability of MC3T3 osteoblast precursor cells were assessed using an MTT-test on days 1, 7, and 10. A significant decrease in cell viability was seen on days 7 and 10 at a PFOA concentration of 100 mcM and above but not at a concentration of 10 mcM. A significant decrease in the alkaline phosphatase activity of osteoblasts was seen at day 7 at a PFOA concentration of 100 mcM and above but not at a concentration of 10 mcM. An increase in calcium and in OCN mRNA was seen at PFOA concentrations of 1 and 10 mcM but not at higher concentrations.

In a second in vitro study investigating the effect of PFOA on osteoclasts, the number of TRACP+ cells containing three or more nuclei was increased at PFOA concentration of 10 mcM and above with evidence for a dose response relationship. Osteoclasts were not significantly affected at 1 mcM. Resorption pit area was significantly increased at a PFOA concentration of 1 mcM, but with no evidence of a dose response relationship and a decrease in pit area with increasing PFOA concentration.

Onishchenko (2011) investigated the administration of PFOA or PFOS at a dose of 0.3 mg/kg/d administered orally via food to pregnant C57BL/6/Bkl mice starting on GD1 to investigate Motor function, circadian activity, and emotion-related behavior in exposed offspring. One pump per litter was sacrificed at birth for brain and liver tissue samples of PFOS and PFOA levels. Offspring were weaned on postnatal day 21 and injected subcutaneously with microtransponders. Test for locomotor and circadian activity were performed at age of 5 to 8 weeks. Animals were tested for emotion-related behavior in elevated plus maze and forced swim test. Test for motor strength and motor coordination were performed in animals at 3 to 4 months old.

Administration of PFOS or PFOA did not affect damn weight gain, litter size, or sex ratio. There were no differences in offspring body or brain weight between groups at birth. Absolute liver weight was increased in PFOA-exposed offspring as compared to controls, but not in PFOS-exposed offspring. Among exposed pups, PFOS concentrations at birth or greater than PFOA concentrations in the brain, but lower in the liver.

PFOS-exposed males walked significantly less than male controls when exploring a new environment, while PFOS-exposed females do not differ from controls. PFOA exposure did not have a significant effect on locomotor activity in either sex.

Circadian activity was measured using the TraffiCage system. During adaptation to the new cage, PFOS-exposed males displayed decreased activity during the first two hours of the test, while PFOS-exposed females displayed decreased activity during the first hour only. PFOA-exposed males were more active during the first hour of the test, while PFOA-exposed females demonstrated decreased activity as compared to controls. After habituation to the cage, PFOS exposure After habituation to the cage, PFOS exposure did not significantly affect activity counts over light or dark periods, either in males or females. PFOA exposed males demonstrated greater activity as compared to controls, especially during the dark phase, while PFOA exposure in females had no effect on activity level. PFOS exposure was associated with a greater number of inactive periods during both light and dark phase in both males and females, although only the difference in females reached statistical significance. PFOA demonstrated an opposite effect, decreasing the number of inactive periods in both light and dark phase which met significance in both phases for males but only in the light phase for females. (see Figure 3)

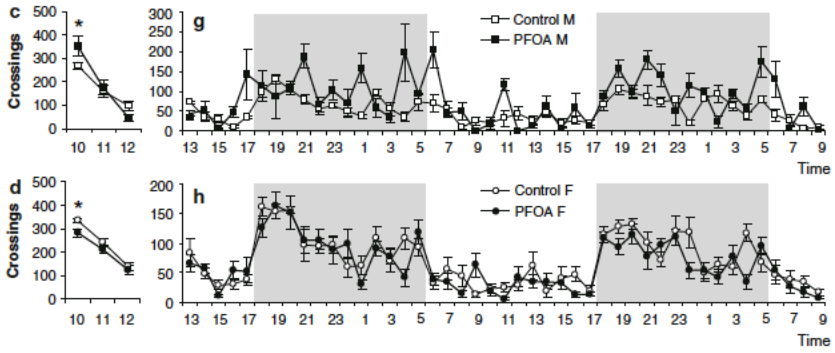

Fig. 2 Novelty-induced (**a–d**) and circadian activity (**e–h**) over 48 h in the home cage and social group in male and female mice prenatally exposed to PFOS or PFOA. Activity counts presented as number of antenna crossings in the TraffiCage (see "Materials and Methods" section for details). Gray areas correspond to a dark phase of the light–dark cycle. * $P < 0.05$, $n = 6$–10)

Figure 3: Figure reproduced from Onishchenko (2011). This was selected as a PFOA critical effect for change in inactive periods seen at 0.3 mg/kg/d (LOAEL). (Onishchenko 2011) The average serum concentration was estimated in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh 2013) using animal species, strain, sex-specific parameters. (ATSDR 2018). Note: because the POD dose and pharmacokinetic model are the same as Koskela (2016), the derived POD serum concentrations are the same.

Evaluation for anxiety-related behavior in the elevated plus maze demonstrated that PFOS-exposed male mice walked less total distance than did controls, which was consistent with previous findings of decreased locomotor activity in this group, but which based on time spent in open and closed arms did not seem to reflect changes in anxiety-related behavior. No significant differences in anxiety-related behavior were noted in PFOS-exposed females or in PFO- exposed males or females.

No effect of PFOA or PFOS was demonstrated in either sex in depression-like behavior in the forced swimming test.

Muscle strength in the hanging wire test was less in PFOS-exposed males who had significantly shorter fall latency than controls. No effect was seen in PFOS-exposed female mice or in PFOA exposure in either sex.

Inconsistent findings were demonstrated between PFOS and PFOA exposure and motor coordination in the accelerating rotarod test. PFOA-exposed females had shorter

fall latency in every trial, but it only met statistical significance in 1 of 4 trials, while PFOA exposed males had similar fall latencies as compared to controls. PFOS-exposed females had shorter fall latency in 2 of 4 trials while PFOS-exposed males had shorter fall latency that was significant in only one of four trials.

4.b. Development of MCLG

Following the approach used by MDHHS and MDH to identify a species-specific DAF, DPAG selected the PFOA serum half-life of 840 days (2.3 years). (Bartell 2010) This was considered more relevant for exposure to the general population than occupational exposure studies used by ATSDR. (ATSDR 2018, Bartell 2010). studied 200 individuals (100 men, 100 women) exposed by drinking PFOA-contaminated water. DAPG used the volume of distribution (Vd = 0.17 L/kg) selected by MDHHS and MDH that was based on human data. (Thompson 2010). These were the references used by EPA in 2016 when they derived a PFOA clearance of 1.4 x 10-4 l/k/d and developed their health advisory level.

DPAG accepted the UFs selected by ATSDR for a UFT of 300. (ATSDR 2018) This resulted in a THSV of 0.028 mg/L for the Goeden Model. Setting the target for the breast fed infant as 0.014 (50%RSC), the MCLG for drinking water is recommended to be 8 ng/L (8PPT) to protect breastfed infants and throughout life. (Figure 4, Table 3)

PFOA	
Dose Response Modeling Method	**LOAEL**
POD	The average serum concentration was estimated in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh 2013) using animal species, strain, sex-specific parameters. (ATSDR 2018)
HED = POD x DAF (mg/kg/d)	DAF = Ke x Vd Ke = 0.000825175 (8.2×10^{-4}) based on a human serum half-life of 840 days (Bartell 2010) Vd = 0.17 L/kg (Thompson 2010) $HED_{LOAEL} = POD_{LOAEL} \times DAF$ $HED_{LOAEL} = POD_{LOAEL} \times Ke \times Vd$ $HED_{LOAEL} = 8.29$ mg/L x 0.0000825175 x 0.17 L/kg $HED_{LOAEL} = 0.001163$ mg/kg/d or 1.163×10^{-3} mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	10 (standard)
Animal to Human (UFA)	3 (DAF applied)
Subchronic to Chronic (UFS)	1 (Chronic effect studied)
LOAEL to NOAEL (UFL)	10 (standard)
Database (UFD)	1
Total Composite (UFT)	300
RfD = HED/UFT (mg/kg/d)	RfD = 0.001163 mg/kg/d/300 RfD = 3.9 ng/kg/day (3.9×10^{-6} mg/kg/d)
THSV = POD / UFT	THSV= 8.29 mg/L/ 300 THSV= 0.028 mg/L
Receptor	Infant exposure via breastmilk for 1 year, from mother chronically exposed via water, followed by lifetime of exposure via drinking water. Protective for short-term, subchronic and chronic. (also protective of formula fed infant). Goeden Model Parameters: Placental transfer of 87% and breastmilk transfer of 5.2% (MDH (2020 PFOA)). The Human Serum half-life is set at 840 days (Bartell 2010).

	The Volume of distribution of 0.17 L/kg (Thompson 2010) Other factors include, 95th percentile drinking water intake, consumers only, from birth to more than 21 years old. Upper percentile (mean plus two standard deviations) breast milk intake rate. Time-weighted average water ingestion rate from birth to 30-35 years of age is used to calculate maternal serum concentration at delivery. (Goeden 2019) A Relative Source Contribution of 50% (0.5) is applied and based on studies which showed that infants RSC is similar to NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants. (CDC 2019)
Chronic Non-Cancer MCLG	The model produces a Chronic Non-Cancer MCLG of 8 ng/L (ppt). This protects health during the growth and development of a breast fed infant. (Figure 4)

Table 3: Development of Non-Cancer MCLG for PFOA

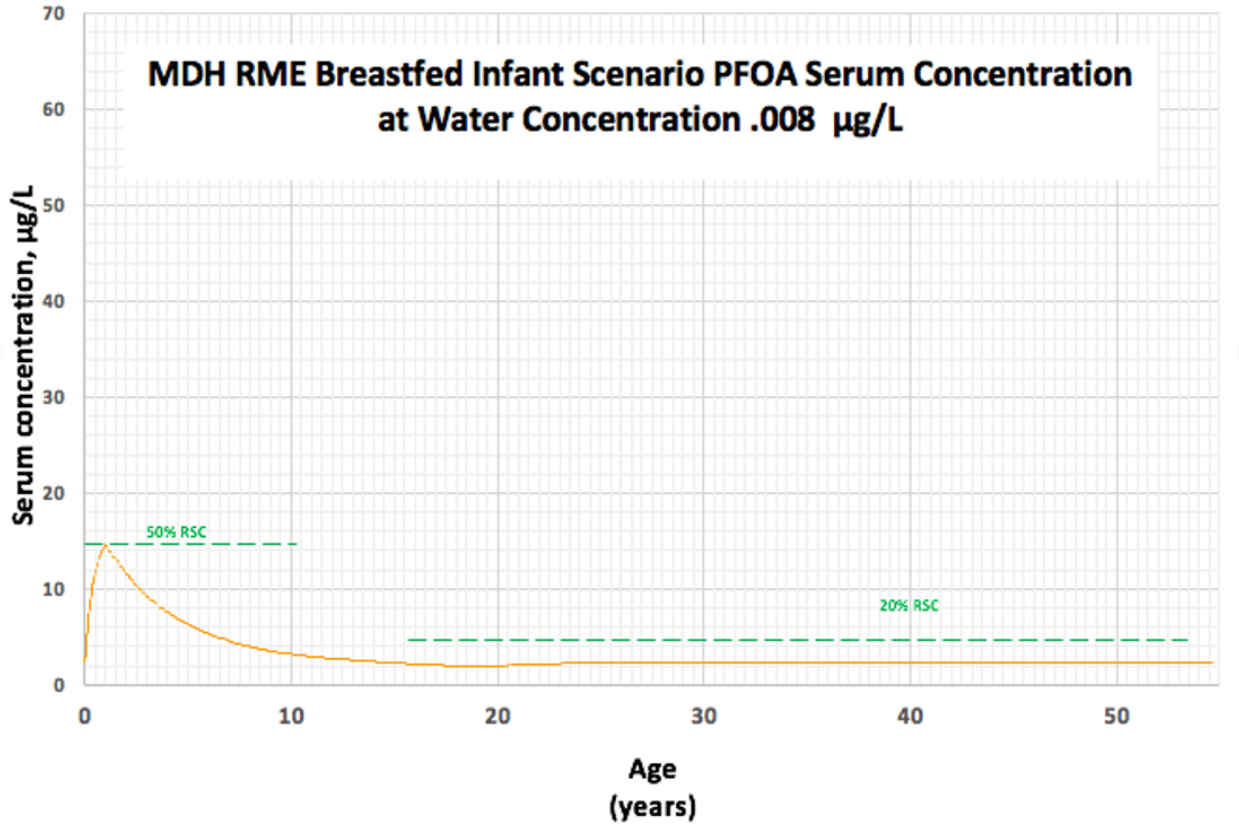

Figure 4. Using the Goeden Model, the POD and its parameters for PFOA were converted to an THSV of 0.028 mg/L. An RSC set at 50% means that half of this (0.014 mg/L) will be from ingested drinking water. The MCLG of PFOA in drinking water should then be set at 0.008 ug/L or 8 PPT to protect from adverse health events.

5. PFOS

After a literature search and a review of the available evidence and recommendations from various agencies, the DPAG developed an MCLG recommendation for PFOS based on Non-Cancer endpoints. DPAG reviewed a number of candidate MRL levels developed by US EPA and ATSDR. (ATSDR 2018, Dong l 2011, Pachkowski 2019, Peden-Adams 2008, Vassiliadou 2010, Butenhoff 2009) Although immune function has not been examined following chronic-duration oral exposure in laboratory animal studies, the lowest LOAEL doses were for immunological effects in intermediate-duration animal studies. These were seen at doses lower than hepatotoxicity or developmental effects. ATSDR did not select an immunotoxicity study as a critical study but did develop a “candidate MRL” using the immunotoxicity study by Dong (2011). The NOAEL endpoint was suppression of natural killer cell activity and anti-Sheep Red Blood Cell Antibody response in mice. Laboratory animal studies, particularly studies in mice, provide supporting evidence of the immunotoxicity of PFOS. Human epidemiological studies are consistent with this evidence as well. After the calculation of HEDs and application of UFs to all of these studies, the resultant MRLs were nearly identical to those using other studies by agencies such as MDHHS. Thus, DPAG concluded the study by Dong l (2011) and the POD of 2.36 mg/L were appropriate. This study was selected over the other immunotoxicity studies because it identified the highest NOAEL for immunotoxicity and the longest exposure duration.

5.a. Review of Critical Study

Dong l (2011) administered PFOS to adult male C57DL6 mice to investigate immunotoxicity outcomes. PFOS with 2% Tween 80 was administered by oral garage daily for 60 days to a targeted total administer dose over that period of 0, 0.5, 1, 5, 25, and 50 mg/kg body weight with controls being administered deionized water with solubilizer only. 12 mice were included in each group. Mice were immunized on the 54th day of PFOS dosing by intravenous injection of sheep red blood cells (SRBC). Six of the 12 mice from each treatment group or sacrificed seven days later and blood was obtained by cardiac puncture. The remaining six mice were administered a booster immunization of SRBC to the right rear foot pad on the final day of PFOS dosing to investigate delayed type hypersensitivity response (DTH) and other immunoglobulin assays.

Mice exposed at the highest dose of 50 mg/kg had significantly lower body weight as compared to controls; however, body weight change was insignificant at other dose levels. Similarly, food intake on the final day of dosing was significantly less at the highest 50 mg/kg dosing group as compared to controls but was there was no significant difference at other dose levels. Relative spleen and thymus weights were decreased at the highest 50 mg/kg dose, but not significantly different than other dose levels. Relative liver weight was increased at both the 25 mg/kg dose and 50 mg/kg dose as compared to controls.

Serum PFOS concentration increased in a dose response fashion with increasing absolute dose administered. There was no significant effect of treatment dose on serum corticosterone level.

IFNgamma level was significantly decreased at the 50 mg/kg dose, without significant changes at other dose levels. IL-4 levels were significantly increased at the 5 mg/kg dose and above. For both IFNgamma and IL-4, changes in levels were largely dose-dependent except at the lowest 0.5 mg/kg dose. The number of cells secreting IL-2 and IL-10 were decreased and increased, respectively, in the 50 mg/kg dose group, but no significant differences were seen at lower dose regimens. As with other cytokines, changes in levels were largely does dependent at the higher dose regimens only.

With respect to immunoglobulin synthesis, IgM levels declined with a dose-response relationship at the 5 mg/kg dose and above. IgG, IgG1, and IgE production were all increased only at the 50 mg/kg dose with other lower dose regimens not affecting serum levels. IgG2a levels and delayed-type hypersensitivity response were unaffected by PFOS administration.

5.b. Development of MCLG

Dong (2011) identified immune suppression, specifically increased IL-4 and decreased Sheep RBC specific IgM levels in the mouse model. Doses administered over 60 days were converted to mg/kg/d by dividing by 60 days. Thus, doses were 0, 0.00833, 0.0167, 0.0833, 0.4167, and 0.8333 mg/kg/d. The NOAEL of 0.0167 mg/kg/day (total dose over 60 days of 1 mg/kg) was selected because it was the highest dose without a statistically significant effect. (Figure 5 is reproduced from Dong (2011; Figure 1)

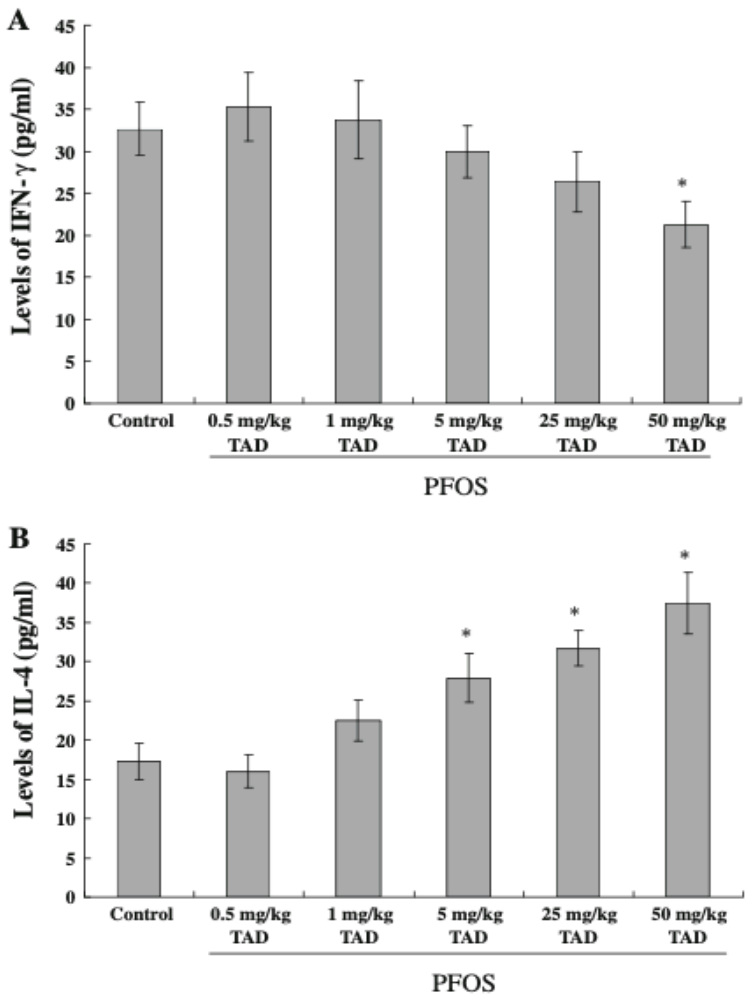

Fig. 1 IFN-γ and IL-4 levels in the splenocyte culture supernatant of splenocytes harvested from mice 24 h after the last of their 60 days of treatment, i.e., daily oral exposures to PFOS. Data are presented as mean ($\pm$SE) of results obtained using ELISA kits. *Significantly different from respective control ($P \leq 0.05$). The data were log transformed as required for statistical analysis. *TAD* Total Administered Dose over the course of 60 days. $n = 6$ in each group

Figure 5: NOAEL critical effect of increased IL-4 levels determined by Dong 2011. The dose administered is over 60 days and is thus converted to the daily dose of 0.0167 mg/kg/day (total dose of 1 mg/kg over 60 days).

Dong provided the serum PFOS level at each dose and thus the 1 mg/kg dose results in a serum PFOS level of 2.36 mg/L (+/- 0.47). This is found in Figure 6.

Table 1 PFOS concentrations in serum (mg/L), body weight, and organ indices in adult male C57BL/6 mice treated with PFOS orally for 60 days

PFOS (mg/kg TAD)	*n*	Serum PFOS (mg/L)	Serum corticosterone (ng/L)	Body weight change[a]	Food intake from day 60 to day 61 (g)	Spleen index[b]	Thymus index[b]	Liver index[b]	Kidney index[b]
Control	6	0.05 ± 0.01	443.28 ± 31.69	4.57 ± 0.42	5.06 ± 0.35	0.45 ± 0.03	0.30 ± 0.03	5.23 ± 0.16	1.48 ± 0.05
0.5	6	1.07 ± 0.11	434.62 ± 28.93	4.81 ± 0.36	5.42 ± 0.42	0.47 ± 0.02	0.27 ± 0.02	5.16 ± 0.14	1.53 ± 0.05
1	6	2.36 ± 0.47	387.14 ± 35.08	5.14 ± 0.45	5.11 ± 0.28	0.46 ± 0.02	0.33 ± 0.02	5.29 ± 0.21	1.57 ± 0.06
5	6	10.75 ± 0.82*	369.87 ± 27.51	4.83 ± 0.34	4.87 ± 0.33	0.46 ± 0.03	0.31 ± 0.02	5.75 ± 0.17	1.54 ± 0.03
25	6	22.64 ± 2.29*	453.76 ± 42.12	3.92 ± 0.47	4.42 ± 0.27	0.42 ± 0.03	0.24 ± 0.02	6.33 ± 0.16*	1.44 ± 0.06
50	6	51.71 ± 3.81*	528.39 ± 33.94	2.16 ± 0.29*	3.39 ± 0.35*	0.35 ± 0.02*	0.21 ± 0.01*	8.04 ± 0.20*	1.41 ± 0.04

PFOS concentrations, body weight (change), and organ weight data did not require transformation for statistical analysis

TAD Total Administered Dose over the course of 60 days

* Indicates that value is significantly different from respective control ($P \leq 0.05$). Data are reported as mean ± SE

[a] Body weight (BW) change denotes change in weight from regimen start to finish: [Postexposure BW (g) − Pre-exposure BW (g)]

[b] Calculated as: [organ weight (g)/body weight (g)] × 100

Figure 6: Serum PFOS level reported by Dong (2011) Table 1.

DPAG followed the approach adopted by MDH and MDHHS and applied the PFOS specific clearance rate of 1241 days (Li 2018) and the EPA reported Vd of 0.23 L/kg to develop the DAF. DPAG agreed with MDHHS application of a UFT of 100. This produced a THSV of 0.024 mg/mL. Setting the target to protect the breast fed infant as 0.012 mg/mL (50%RSC), the MCLG for drinking water is recommended to be 8 ng/L (8PPT) to protect breast fed infants and throughout life. (Figure 7, Table 4)

PFOS	
Dose Response Modeling Method	**NOAEL**
POD	2.36 µg/mL(or 2.36 mg/L)
HED = POD x DAF (mg/kg/d)	Toxicokinetic Adjustment based on Chemical- Specific Clearance Rate (Li 2018, MDH 2020 PFOS) DAF = Vd (L/kg) x (Ln2/Half-life, days) DAF = 0.23 L/kg x (0.693/1241 days) = DAF = 0.00013 L/kg/d HED = POD x DAF (mg/kg/d) HED = 2.36 mg/L x 0.00013 L/kg/d HED = 0.000307 mg/kg/d

Uncertainty Extrapolation	
Human Variability (UFH)	10
Animal to Human (UFA)	3 (DAF applied)
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	1
Database (UFD)	3
Total Composite (UFT)	100
RfD = HED/UFT (mg/kg/d)	RfD = HED/UFT (mg/kg/d) RfD = 0.000307 mg/kg-d/100 RfD = 3.1 ng/kg/d or 3.1x 10^{-6} mg/kg-d
THSV = POD/UFT	TSHV = 2.36 mg/L/100 TSHV = 0.024 mg/mL
Receptor	Infant exposure via breastmilk for 1 year, from mother chronically exposed via water, followed by lifetime of exposure via drinking water. Protective for short-term, subchronic and chronic. The 95th percentile water intake rates (Table 3-1 and 3-3, USEPA 2019) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2019) were used. Breast-fed infant, which is also protective of a formula-fed infant using Minnesota Department of Health Model based on Goeden (2019). Placental transfer of 40% (MDH 2020 PFOS). Breastmilk transfer of 1.7% (MDH 2020 PFOS). Human Serum half-life of 1241 days (Li 2018) Volume of distribution of 0.23 L/kg (USA EPA 2016c) 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden [2019]) Upper percentile (mean plus two

	standard deviations) breast milk intake rate (Goeden 2019) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden 2019)
Chronic Non-Cancer MCLG	The model produces a Chronic Non-Cancer MCLG of 14 ng/L (ppt). This protects health during the growth and development of a breast fed infant. Figure 7

Table 4: Development of Non-Cancer MCLG for PFOS

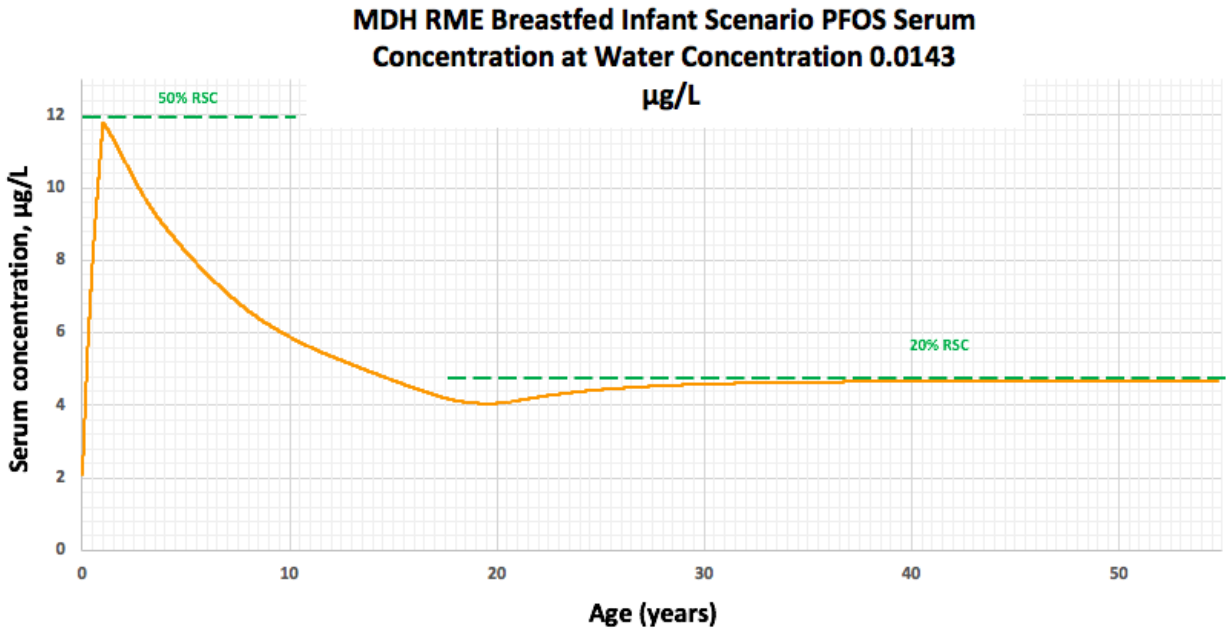

Figure 7. Using the Goeden Model, the reference dose and its parameters for PFOS were converted to an THSV of 0.024 mg/L. An RSC set at 50% means that half of this (0.012 mg/L) will be from ingested drinking water. The MCLG of PFOS in drinking water should then be set at 0.014 ug/L or 14 PPT to protect the breast fed infant from adverse health events.

6. PFNA

After a literature search and a review of the available evidence and recommendations from various agencies, the DPAG developed an MCLG recommendation for PFNA based on Non-Cancer endpoints. The critical study identified was Das (2015). ATSDR released a provisional minimal risk level for intermediate exposure based on an analysis of Das (Das 2015, Rogers 2014, Wolf 2010). The HED of the NOAEL of 1 mg/kg/d identified in the Das (2015) developmental toxicity study was selected as the POD for the ATSDR MRL. At this dose, there was no statistical difference from controls for developmental landmarks of eye opening, preputial separation in makes, and vaginal opening in females. A TWA serum PFNA concentration was estimated for dams using the serum concentration in the control group (0.015 µg/mL) as the baseline concentrations and the terminal concentration for the 1 mg/kg/d group (13.67 µg/mL) resulting in an estimated TWA serum concentration of 6.8 µg/mL. Das (2015) provided the serum concentrations directly to the ATSDR. NJDEP (2015) used the same study and the same dose of 1 mg/kg/d, but as a LOAEL for increased liver weight in pregnant mice. DPAG studied the controversy surrounding liver weight and similar effects produced by expression of peroxisome proliferator-activated receptor-alpha (PPARalpha) which is specific to rodents. DPAG agreed with ATSDR's selected POD and further agreed with Michigan's application of the Goeden transgenerational toxicokinetic model to this POD. Interestingly, the resulting MCLG is lower than the MCL determined by NJDEP (2015).

6.a. Summary of Critical Study

This study administered PFNA to pregnant CD-1 mice by oral gavage daily on gestational day 1 - 17 to assess for developmental toxicity outcomes. Treatment groups included 1 mg/kg/d, 3 mg/kg/d, 5 mg/kg/d, and 10 mg/kg/d while controls received deionized water. Mice were allocated to two groups: one group was sacrificed on GD 17 for analysis of gravity uterus, live fetuses, and maternal and fetal liver analysis. The second group was allowed to give birth and pregnancy outcomes and postnatal survival, growth, and development of the pups were monitored.

Mice in the highest 10 mg/kg/d dose group demonstrated overt toxicity beginning on GD 8. Therefore, the highest dose utilized for the remainder of the study was 5 mg/kg/d. The 3 mg/kg/d and 5 mg/kg/d groups demonstrated increased maternal weight gain as compared to controls for GD 11 to GD 17 which of the authors opined was likely due to dose-related enlargement of maternal liver. Increases in absolute and relative liver weight were seen at necropsy on GD 17 at the 1 mg/kg/d, 3 mg/kg/d, and 5 mg/kg/d doses. These changes demonstrated a dose response relationship in pregnant mice but not in non-pregnant mice. The authors noted that liver enlargement is common to PFAA exposure and it's probably mediated by activation of the PPARalpha signaling pathway.

With respect to pregnancy outcomes, there was no effect of treatment group on number of implants, number of life fetuses, or fetal weights. Absolute and relative liver weight was increased in PFNA exposed fetuses as compared to controls; however, there was no dose-response relationship. There was no effect of treatment group on

skeletal or visceral examination of fetuses. Full litter resorption occurred at the 10 mg/kg dose; however, this was associated with overt maternal toxicity, as noted above.

Postnatal survival of pups was decreased at the 5 mg/kg/d dose with deaths starting on PND 2 and only 20% of pups surviving to weaning. Treatment at the two lower dose levels did not affect pup survival. Exposure at the 3 mg/kg/d and 5 mg/kg/d was associated with decreased weight gain in pups with a dose response relationship. Decreased body weight was more persistent in male pups without any evidence of catch up growth in the post weaning period, whereas females typically recovered to control levels by 7 weeks of age. Relative liver weight was increased in pups at all treatment levels as compared to controls. This effect became less strong in the post weaning period and at PND 70 no significant effects remained. There were dose-dependent delays in postnatal development in the 3 mg/kg/d and 5 mg/kg/d groups with respect to eye opening, preputial separation, and vaginal opening.

Analysis of liver mRNA transcripts demonstrated PPARalpha-dependent gene expression in both fetal and neonatal mouse liver with activation of other transcripts regulated by other pathways. PPARalpha activation persisted to young adulthood and then declined, which the authors attributed to body burden of PFNA.

6.b. Development of MCLG

The HED of the NOAEL of 1 mg/kg/d identified in the Das (2015) developmental toxicity study was selected as the POD for the MRL. At this dose, there was no statistical difference from controls for developmental landmarks of eye opening, preputial separation in makes, and vaginal opening in females. (Figure 8)

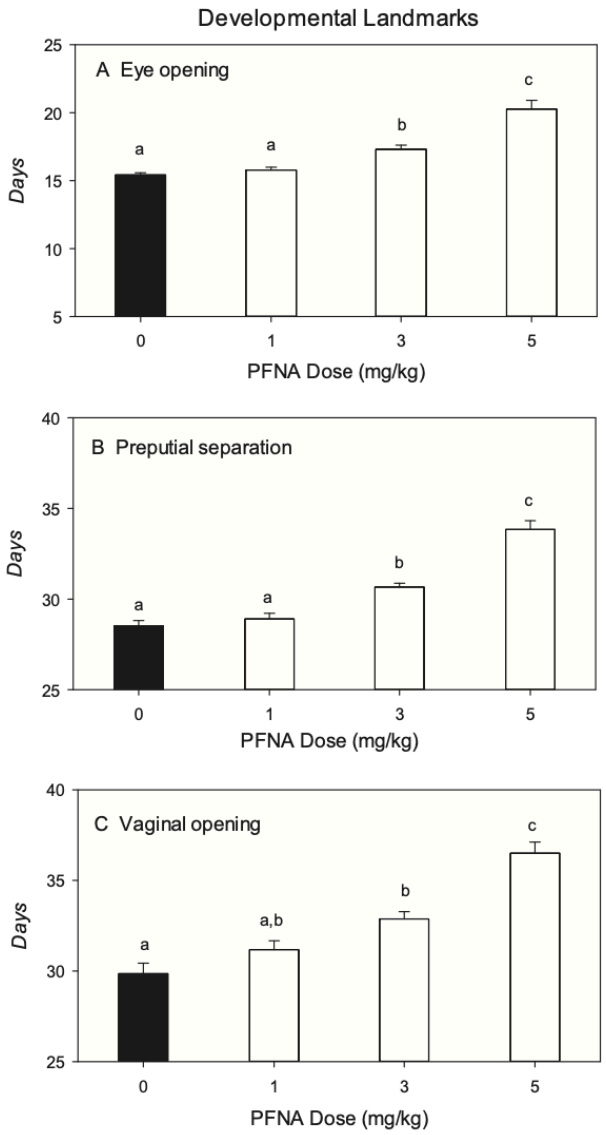

Fig. 9. Developmental landmarks of mouse offspring exposed to PFNA. Panel (A) illustrates eye opening, panel (B) preputial separation in males and panel C vaginal opening in females. ANOVA indicated a significant treatment effect. Points represent means ± S.E. of 6–13 litters. Different letters denote significant differences ($p < 0.05$) among exposure groups determined by Tukey–Kramer test.

Figure 8: PFNA NOAEL of 1 mg/kg identified by Das (2015)

A TWA serum PFNA concentration was estimated for dams using the serum concentration in the control group (0.015 µg/mL) as the baseline concentrations and the terminal concentration for the 1 mg/kg/d group (13.67 µg/mL) resulting in an estimated

TWA serum concentration of 6.8 µg/mL. Das provided the serum concentrations directly to ATSDR. (ATSDR 2018) DPAG agreed with ATSDR's selected POD and UFTs and further agreed with MDH DAF calculations and the use of Goeden transgenerational toxicokinetic model to this POD. Setting the target to protect the breast fed infant as 0.0115 mg/mL (50%RSC), the MCLG for drinking water is recommended to be 6 ng/L (6 PPT) to protect breast fed infants and throughout life. (Figure 8, Table 5)

PFNA	
Dose Response Modeling Method	**NOAEL**
POD	A NOAEL of 1 mg/kg/d was identified for developmental effects. Das (2015) The average serum concentration for NOAEL (1 mg/kg/d) was estimated (6.8 mg/L) in dams using an empirical clearance model (Wambaugh 2013).
HED_{NOAEL} = POD x DAF (mg/kg/d)	DAF = Ke x Vd Ke = 0.000489165 (4.8×10^{-4}) based on a human serum half-life of 1417 days. The human serum half-lives were an arithmetic mean of 2.5 years (913 days) for 50 year old or younger females and 4.3 years (1570 days) for females older than 50 years old and all males. An average of 3.9 years (1417 days) was calculated based on those averages. (calculated from Zhang 2013) Vd = 0.2 L/kg (ATSDR 2018; Ohmori 2003) HED_{NOAEL} = POD x DAF (mg/kg/d) HED_{NOAEL} = POD x Ke x Vd HED_{NOAEL} = 6.8 mg/L x 0.000489165 x 0.2 L/kg HED_{NOAEL} = 0.000665 mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	10
Animal to Human (UFA)	3
Subchronic to Chronic (UFS)	1
LOAEL to NOAEL (UFL)	1
Database (UFD)	10
Total Composite (UFT)	300 (as per ATSDR 2018)
RfD = HED/UFT (mg/kg/d)	RfD = HED/UFT (mg/kg/d) RfD = 0.000665 mg/kg/d / 300 RfD = 2.2 ng/kg/day (2.2 x 10-6 mg/kg/d)
THSV = POD/UFT	THSV = POD/UFT THSV = 6.8 mg/L / 300

	THSV = 0.023 mg/L
Receptor	Breast-fed infant, which is also protective of a formula-fed infant Placental transfer of 69%. Breastmilk transfer of 3.2% (MDH 2020) Half-life = 1417 days (3.9 years). (Zhang 2013, MDDHS 2019, ATSDR 2018) Volume of distribution = 0.2 L/kg (ATSDR 2018, Ohmori 2003). Applied to the Goeden Model. 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden 2019) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden 2019) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden 2019) Relative Source Contribution of 50% (0.5) Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)
Chronic Non-Cancer MCLG	The model produces a Chronic Non-Cancer MCLG of 6 ppt. This protects health during the growth and development of a breast fed infant. Figure 8

Table 5: Development of Non-Cancer MCLG for PFNA

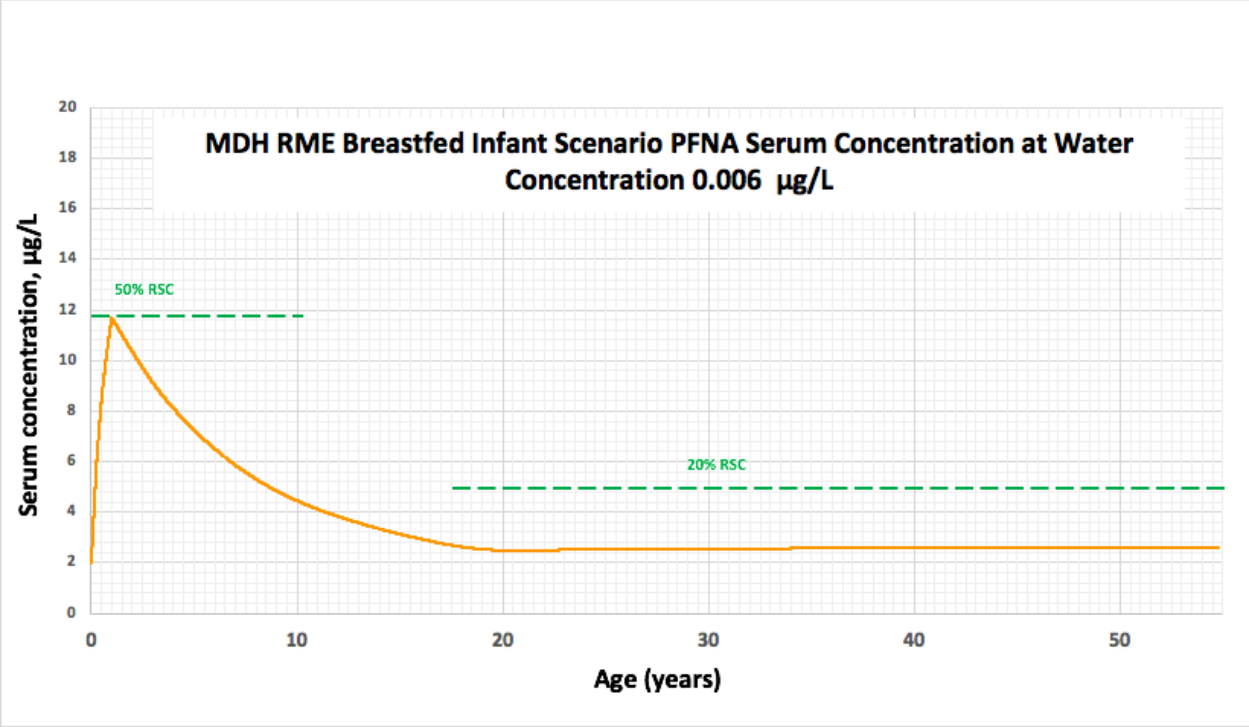

Figure 9. Using the Goeden Model, the reference dose and its parameters for PFNA were converted to an THSV of 0.023 mg/L. An RSC set at 50% means that half of this (0.0115 mg/L) will be from ingested drinking water. The MCLG of PFNA in drinking water should then be set at 0.006 ug/L or 6 PPT to protect from adverse health events.

7. PFHXs

After a literature search and a review of the available evidence and recommendations from various agencies, the DPAG developed an MCLG recommendation for PFHxS based on Non-Cancer endpoints. The critical study selected was Chang S (2018). This study identified reduced litter size following a 14 day prior to pregnancy oral exposure in Adult CD-1 female mice. Serum levels were measured at 14 days. MDHHS (MDHHS (2020 PFHXS) and NTP (2018) identified a POD of 32.4 mg/L serum concentration for male rats based on $BMDL_{20}$ analysis of this study. DPAG had selected a BMR of 10% (hence $BMDL_{10}$) as the preferred method for using BMD to select a POD and therefore rejected the use of $BMDL_{20}$. NHDES and Ali (2019) provided rigorous and more recent analysis and used a BMR of 50% of the Standard Deviation ($BMDL_{0.5SD}$). This was in keeping with EPA guidance on the selection criteria for BMRs and so was acceptable to the DPAG. The $BMDL_{0.5SD}$ derived by Ali (2019) using data from the critical study was 13.9 mg/mL and provided the basis for the MCLG.

7.a. Summary of Critical Study

This study administered potassium perfluorohexanesulfonate (PFHxS) to CD-1 mice to assess for reproductive and developmental toxicity. Both male and female mice were assigned to one of four treatment groups: control, 0.3 mg/kg/d, 1 mg/kg/d, and 3 mg/kg/d with 30 mice of each sex assigned to each treatment group. Following an acclimation period that included observation of female mice for estrous cyclicity, male

and female mice were administered vehicle control or aqueous solution of PFHxS by oral gavage daily beginning 14 days prior to cohabitation. Males were administered vehicle or treatment for a total of at least 42 days with scheduled sacrifice one day post-last dose. F_0 females were administered vehicle or treatment until lactation day 21 with scheduled sacrifice one day later. After weaning on postnatal day 21, F_1 offspring were directly dosed with PFHxS for an additional 14 days at the same respective maternal dose.

F_0 mice were observed daily for clinical signs of toxicity before and 2 hours after oral gavage dosing. No signs of clinical toxicity were noted at any of the treatment levels. Body weights and food consumption were recorded weekly. There was a significant body-weight gain in male mice at the 0.3 mg/kg/d and 1 mg/kg/d dose levels but not at the 3 mg/kg/d dose; therefore, this was not considered to be treatment-related. There were no significant differences in body-weight gain in female mice across all treatment groups. There was no significant difference in food consumption across all treatment groups in either sex.

Functional observational battery and motor activity assessment was performed on 10 mice/sex/treatment group prior to scheduled sacrifice and no significant differences were noted across the treatment groups in any of the measured outcomes or in trend of motor activity over time.

Among F_0 mice, there was no significant difference among treatment groups with respect to any of the reproductive function outcomes investigated. In males, PFHxS did not affect sperm motility, count, density, and morphology. In females, PFHxS did not affect mating index, fertility index, or precoital interval.

With respect to pregnancy outcomes in F_0 mice, there was no significant difference between treatment groups in number of implantations, mean gestation length, number of dams with viable pups, pops born to implant ratio, and sex ratio. The number of pups born per litter and mean live litter size was significantly reduced in the 1 mg/kg/d and 3 mg/kg/d as compared to controls. The authors opined that the toxicological significance of that fighting was unclear due to 1) the lack of a dose response relationship; 2) no significant difference in pup to implant ratio among treatment groups; and 3) the lack of other negative effects on developmental or reproductive outcomes.

At F_0 mice necropsy, there was no significant findings on macroscopic examinations across treatment groups. With the exception of liver weight, there was no difference across treatment groups on absolute or relative organ weights as compared to controls. PFHxS was associated with a significant, dose-dependent increase in both absolute and relative liver weight at the 1 mg/kd/d and 3 mg/kg/d in both male and female mice. This was considered to be an adaptive response.

With the exception of liver tissue, there was no difference across treatment groups in tissue histology. Liver tissue demonstrated primarily centrilobular hepatocellular hypertrophy among treatment groups with a dose-response relationship. In male mice only at the highest 3 mg/kg/d dose, mild microvesicular fatty change and minimal single-cell necrosis was noted in 6 of 10 and 4 of 10 mice, respectively. In female mice only at the highest 3 mg/kg/d dose, a low incidence of cytoplasmic vacuolation was seen in 3 out of 10 mice. Liver tissue findings were considered by the authors to be consistent with an adaptive response.

There was no difference between F_0 treatment groups with any hematology parameters or with serum TSH levels. And male mice only at the highest 3 mg/kg/d dose, there was a significant decrease in serum total cholesterol and bilirubin and a significant increase in alkaline phosphatase. This was considered to be an adaptive change related to increased metabolism of the parasites and unlikely to be of toxicological significance. There were no other significant differences in male mice in clinical chemistry parameters or in female mice in any clinical chemistry parameters.

Among F_1 mice, there was no significant difference between treatment groups on pub survival, body weight at birth or anytime thereafter, balanopreputial separation in males, vaginal patency in females, or areolae/nipple analgen retention in males. In male pups, a significantly increased anogenital distance was seen at all treatment levels as compared to controls; when adjusted to cube root body weight, a significantly increased anogenital distance was seen at the 0.3 mg/kg/d and 3 mg/kg/d treatment levels but not the 1 mg/kg/d treatment level. Among female pups, a decreased anogenital distance relative to cube root body weight was seen at the 1 mg/kg/d treatment level but no other treatment groups. The authors opined that these findings should not be considered toxic logically relevant in that no dose-response relationship was seen and that shortening of the anogenital distance rather than lengthening is indicative of anti-androgenic activity.

At F_1 mice necropsy, with the exception of liver and thyroid weight, there was no difference across treatment groups on absolute or relative organ weight as compared to controls. Absolute liver weight was significantly increased in males at the highest 3 mg/kg/d dose on PND 36 and relative liver weight was increased at the highest 3 mg/kg/d dose in males and females on PND 21 and 36. This was considered an

adaptive response. And female mice only at the highest 3 mg/kg/d dose, there was a significant increase in relative thyroid weight at PND 36 only but not on absolute thyroid weight. However, there were no thyroid histological abnormalities including hypertrophy in that group and no corresponding change in serum TSH levels.

With the exception of liver tissue, there was no difference across treatment groups in tissue histology. Liver tissue demonstrated mild centrilobular hepatocellular hypertrophy in both male and female pups with no evidence of necrosis. This was considered an adaptive response.

Analysis of liver mRNA transcript levels in F_0 and F_1 mice demonstrated increased transcripts that are sensitive to PPAR-alpha activation and CAR activation in the high-dose treatment group as compared to controls across both sexes in F_0 and F_1 mice. Cyp3a11, which is associated with PXR activation, was increased in the high-dose treatment group in F_0 males and F_1 pups of both sexes. Transcripts associated with fatty acid metabolism were increased in the high-dose treatment group across both sexes in F_0 and F_1 mice. However, transcripts associated with cellular stress were not increased.

A second toxicokinetic study was performed by the authors to determine serum and liver PFHxS concentrations at the same daily doses as the main study. The toxicokinetic study was divided into two subsets: 5 mice/sex/dose were administered PFHxS at 0.3 mg/kg/d, 1 mg/kg/d, and 3 mg/kg/d or vehicle control for 14 days prior to scheduled sacrifice. 7 mice/sex/dose were administered PFHxS at 0.3 mg/kg/d, 1 mg/kg/d, and 3 mg/kg/d or vehicle control for 14 days prior to cohabitation. Male mice were dosed for an additional 14 days with scheduled sacrifice one day post-last dose. Female mice were dosed through mating and gestation with scheduled sacrifice on gestation day 18.

Serum and liver sample collections were obtained at necropsy for male and female mice. For fetal serum and liver concentrations, pooled fetal blood and liver sample by litter were obtained at necropsy. The toxicokinetic study found that steady state observations for PFHxS were similar to that seen for PFOS as previously reported in rodent and monkey studies.

The authors concluded that it all doses studied, there was no effect of PFHxS on body weight, food consumption, estrus cyclicity, mating, fertility, gestation length, spermatogenesis, or macro and microscopic evaluation of reproductive organs in F_0 mice. A slight decrease in live litter size what is considered equivocal due to no dose response relationship and no change in the pump to implant ratio. Among F_1 mice, there was no effect of PFHxS on survival, birthweight, or reproductive development. Changes in liver weight, liver tissue microscopy, and clinical chemistry findings were all considered to be adaptive in nature.

7.b. Development of MCLG

The $BMDL_{0.5SD}$ derived by (Ali 2019) using data from the critical study of Chang (2018) was 13.9 mg/mL and provided the basis for the MCLG. (Figure 9)

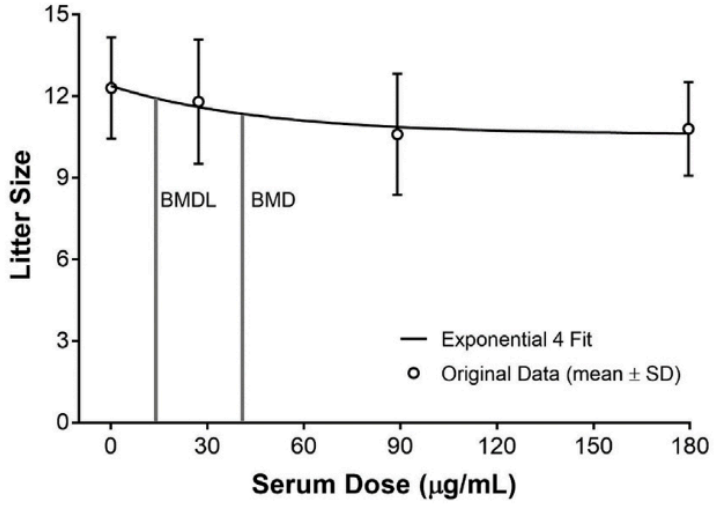

Fig. 2. Reduced litter size in female mice after 14-day oral exposure to K^+PFHxS based on summarized data from Chang et al. (2018). The curve is calculated using the normal, constant variance exponential model. In this model, the BMD is the concentration that elicits a response 0.5 times the standard deviation below the mean of the tested population. The BMDL is the concentration corresponding to the lower 95% confidence interval.

Figure 10: $BMDL_{0.5SD}$ derived by Ali (2019) of 13.9 mg/mL using data from the critical study of Chang (2018).

DPAG agreed with the DAF, UFTs, and application of the Goeden Model by MDH and MDHHS. Setting the target to protect the breast fed infant as 0.023 mg/mL (50%RSC), the MCLG for drinking water is recommended to be 20 ng/L (20 PPT) to protect breast fed infants and throughout life. (Figure 10, Table 6)

PFHxS	
Dose Response Modeling Method	**lower confidence limit on the BMD on 50% of the SD ($BMDL_{0.5SD}$)**
POD	13.9 mg/mL
HED = POD x DAF	DAF based on Chemical-Specific Clearance Rate DAF = Vd (L/kg) x (Ln2/Half- life, days) DAF = 0.25 L/kg x (Ln2/1935 days) DAF = 9.0 x 10^{-2} mL/kg/d HED = POD x DAF HED = 13.9 mg/mL x 8.61x10^{-2} mL/kg/d HED = 1.196 x 10^{-3} mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	10
Animal to Human (UFA)	3 based on application of DAF
Subchronic to Chronic (UFS)	3 based on extrapolation from Chang S (2018)
LOAEL to NOAEL (UFL)	1
Database (UFD)	3 based on small number of studies
Total Composite (UFT)	300
RfD = HED/UFT (mg/kg/d)	Reference Dose = HED /UFT Reference Dose = 1.196 x 10^{-3} mg/kg/d / 300 Reference Dose = 3.98 ng/kg/d (rounded to 4.0 ng/kg/d)
ITHSL = POD / UFT	ITHSL = 13.9 mg/mL / 300 ITHSL = 0.0463 mg/mL
Receptor	Breast-fed infant, which is also protective of a formula-fed infant. Placental transfer of 70% (MDH 2020 PFHXS). Breastmilk transfer of 1.4% (Li 2019). Half-life = 1935 days. Vd = 0.25 L/kg (USEPA 2016, Han 2012). 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden [2019]) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden 2019) Time-

	weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden 2019) Relative Source Contribution of 50% (0.5). Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)
Chronic Non-Cancer MCLG	The model produces a Chronic Non-Cancer MCLG of 20 ppt. This protects health during the growth and development of a breast fed infant.

Table 6: Development of Non-Cancer MCLG for PFHxS

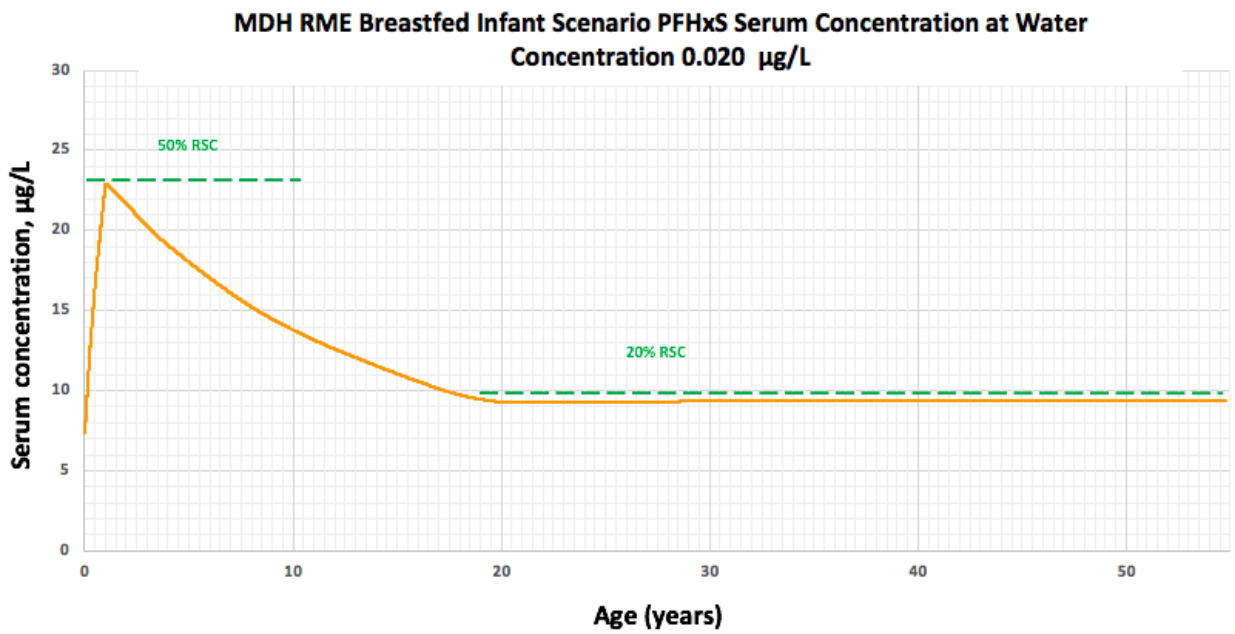

Figure 11. Using the Goeden Model, the reference dose and its parameters for PFHxS were converted to an THSV of 0.046 mg/L. An RSC set at 50% means that half of this (0.023 mg/L) will be from ingested drinking water. The MCLG of PFHXS in drinking water should then be set at 0.020 ug/L or 20 PPT to protect from adverse health events.

8. PFHpA

PFHpA is a difficult compound to develop advisories for because there is a paucity of evidence on its toxicity. The DPAG decided to base recommendations on its chemical structure. MDHHS (2019) has made similar recommendations for other PFAS that lack sufficient scientific evidence to form conclusions about health advisory levels. Like PFOA, PFHpA is a carboxylic acid. PFHpA is a 7-carbon molecule and PFOA is an 8 carbon molecule. The DPAG concludes that the MCLG for PFHpA should be conservatively set at the same threshold for PFOA – 8 PPT.

9. PFBS

After a literature search and a review of the available evidence and recommendations from various agencies, the DPAG developed an MCLG recommendation for PFBS based on Non-Cancer endpoints. The DPAG identified Feng 2017 as the critical study. The ATSDR 2018 considered the available data inadequate for identifying a critical endpoint and evaluating dose-response relationships but did not review Feng 2017. USEPA (2018 PFBS) selected Lieder (2009) and the critical effect of papillary tubular ductal epithelium hyperplasia in P0 females. They applied BMD with a BMR of 10%. The derived $BMDL_{10}$ (HED) of 11.5 mg/kg/d was modified with a UFT of 1000 to achieve a reference dose of 1x10-2 (mg/kg/d). Interestingly, USEPA (2018 PFBS) identified the decreased serum total T4 in newborn (PND 1) mice from Feng 2017 as a critical effect and performed a BMD modeling, but selected a BMR of 20%

over control response rate. The modeled $BMDL_{20}$ and applied a UFT of 300 achieved the same reference dose of 1x10-2 (mg/kg/d) as the kidney critical effect from Lieder 2009. MDHHS identified the kidney effects as a potentially compensatory response and thought the thyroid effects had greater functional significance. However, they removed the allometric scaling used in the draft USEPA (2018 PFBS) and applied the PFBS specific DAF developed by MDH. Thus, MDHHS was able to develop a chemical specific HED. However, MDH did use the $BMDL_{20}$ identified by the US EPA to calculate their HED. DPAG chose to continue with use of the $BMDL_{10}$ as the standard approach where the model fit was valid and used the USEPA (2018 PFBS) BMD modeling which, in addition to the $BMDL_{20}$, included a calculated $BMDL_{10}$ of 1.84 mg/kg/d. This $BMDL_{10}$ POD HED of 1.84 mg/kg/d was divided by 0.149 to remove the DAF employed by USEPA (2018 PFBS) prior to subjecting the data to BMD analysis (USEPA 2018 PFBS). This results in a POD of 12.35 mg/kg/d. DPAG agreed with the application of half-life ratios by MDH of the new chemical specific DAF of 316 (human serum half-life/female mouse serum half-life = 665 hours/2.1 hours = 316). (MDH 2020 PFBS) Dividing by the new chemical specific DAF of 316 (human serum half-life/female mouse serum half-life = 665 hours/2.1 hours = 316) results in a HED of 0.039 mg/kg/d.

9.a. Review of Critical Study

This study investigated the effects of prenatal perfluorobutanesulfonate (PFBS) exposure on perinatal growth and development, people on site, and reproductive and thyroid endocrine system function in female ICR mice. PFBS potassium salt was administered orally to pregnant mice at doses of 50, 200, and 500 mg/kg/d from GD1 to

GD20. Administration of the test substance did not affect weight gain, fetal loss, or behavior of the dams at the doses studied. 30 dams were assigned to one of three experimental groups: 1) sequential examination of perinatal survival and growth, pubertal onset, and ovarian and uterine development; 2) hypothalamic-pituitary-gonadal hormone and hypothalamic pituitary thyroid hormone measurements at postnatal days 1, 30, and 60; 3) measurement of serum levels of PFBS.

Postnatal day 1 body weights of female offspring at the 200 mg/kg/d dose and above were decreased relative to controls. These dose groups remained underweight throughout weaning, pubertal, and adult periods. Delays in eye-opening, vaginal opening, and first estrous period were seen in female offspring at the 200 mg/kg/d dose and above with a dose response relationship.

Absolute and relative ovary weight were decreased at the 200 mg/kg/d dose and above, although no dose response relationship was seen. Number of primordial follicles, primary follicles, secondary follicles, early actual follicles, enter follicles, pre-ovulatory follicles, and corpora lutea were decreased at the 200 mg/kg/d dose and above, although no dose response relationship was seen.

Absolute and relative uterine weight were decreased at the 200 mg/kg/d dose and above, although no dose response relationship was seen. Total uterine diameter, endometrial thickness, and myometrial thickness were decreased at the 200 mg/kg/d dose and above, with a minimal dose response relationship.

Number of days spent in diestrus stage were significantly increased in female offspring at the 200 mg/kg/d dose and above as compared to controls, although no dose response relationship was seen. Levels of serum E2 were decreased at the 200

mg/kg/d dose and above on postnatal day 30 and 60 but not on postnatal day 1 and with no dose response relationship. Levels of luteinizing hormone (LH) were decreased at the 200 mg/kg/d dose and above on postnatal day 30 but not on postnatal day 1 or 60 with no discernible dose response relationship. Levels of P4 were decreased at the 200 mg/kg/d dose and above on postnatal day 60 but not on postnatal day 1 or 30 with no discernible dose response relationship. Levels of gonadotropin-releasing hormone (GnRH) were not affected at any of the doses studied.

Total T3 and total T4 was significantly decreased in female offspring at the 200 mg/kg/d dose and above on postnatal day 1, 30 and 60, although no clear dose response relationship was seen. TSH and hypothalamic *Trh* mRNA were both increased at the 200 mg/kg/d dose and above on postnatal day 30, but not on postnatal day 1 or 60. In dams, total T4, total T3, free T4 were decreased and TSH was increased at the 200 mg/kg/d dose and above without an obvious dose response relationship.

9.b. Development of MCLG

DPAG agreed with USEPA selection of a decreased serum total T4 in newborn (PND 1) mice from Feng 2017 but used the USEPA reported $BMDL_{10}$ of 1.84 mg/kg/d.

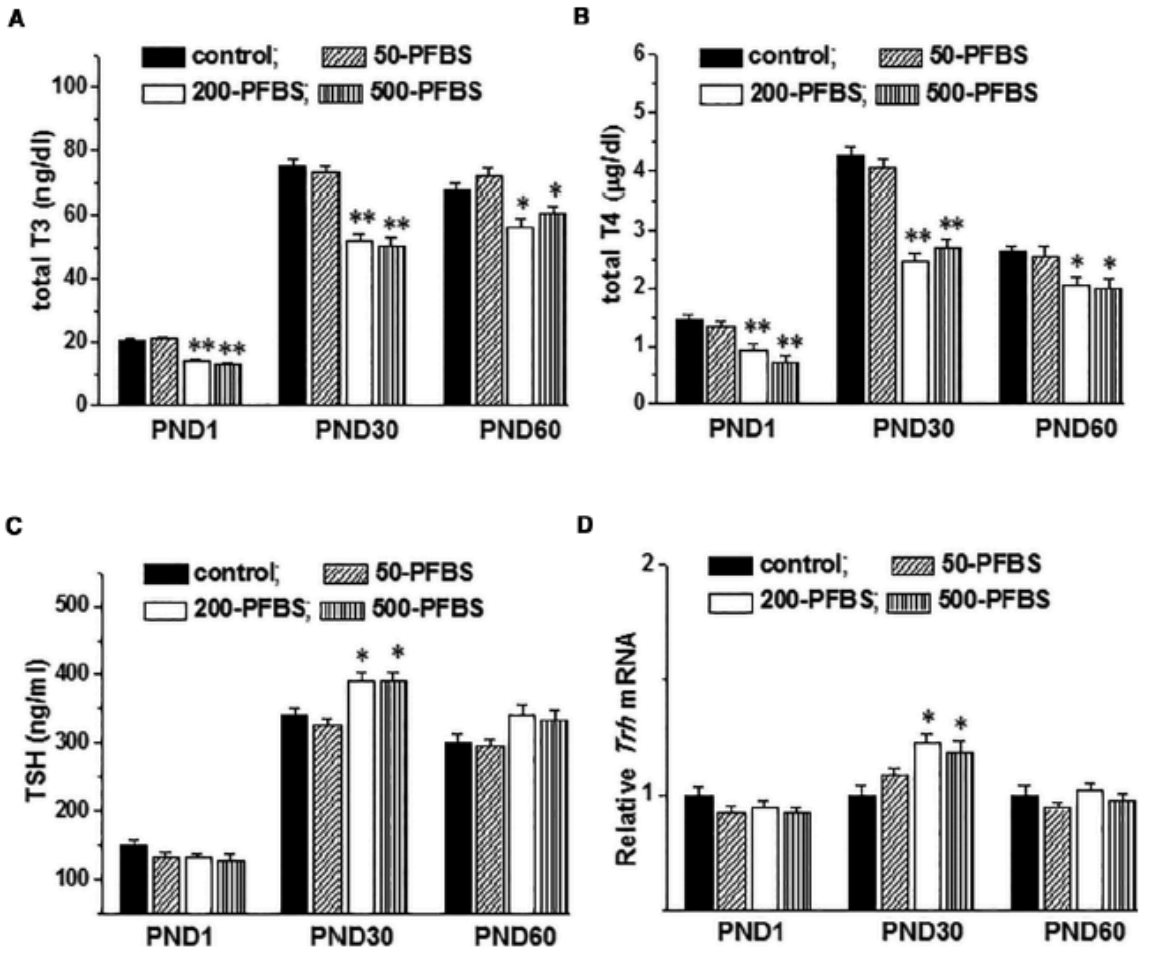

FIG. 4. Influence of prenatal perfluorobutanesulfonate (PFBS) exposure on hypothalamic–pituitary–thyroid hormone levels. Bar graphs show the levels of serum total 3,3′,5-triiodothyronine (T3) (A), total thyroxine (T4) (B), thyroid-stimulating hormone (TSH) (C) and hypothalamic *Trh* mRNA (D) in postnatal day (PND) 1, PND30, and PND60 control offspring and PFBS-offspring. *$P < 0.05$ and **$P < 0.01$ versus control offspring (1-way ANOVA).

Figure 12: Critical effect of PFBS on total thyroxine (T4) levels identified by Feng 2017 used to develop $BMDL_{10}$ POD.

This $BMDL_{10}$ POD HED of 1.84 mg/kg/d was divided by 0.149 (USEPA 2018 PFBS) page F-10 to F-13) to remove the DAF employed prior to subjecting the data to BMD analysis (USEPA 2018 PFBS). This results in a POD of 12.35 mg/kg/d. Dividing by the chemical specific DAF of 316 (human serum half-life/female mouse serum half-life = 665 hours/2.1 hours = 316) (MDH 2020 PFBS) results in a HED of 0.039 mg/kg/d. DPAG agreed with the UFT applied by USEPA. Applying the USEPA ingestion rate for

birth to < 1 year old and a conservative 20% RSC, the MCLG for drinking water is recommended to be 55 ng/L (55 PPT) to protect infants and throughout life. (Table 7)

PFBS	
Dose Response Modeling Method	**$BMDL_{10}$**
POD HED Units	US EPA reported $BMDL_{10}$ of 1.84 mg/kg/d. This was divided by 0.149 (USEPA 2018 PFBS) to derive a POD of 12.35 mg/kg/d.
POD x DAF = HED	DAF = (human serum half-life/female mouse serum half-life) DAF = 665 hours/2.1 hours DAF = 317 (MDH 2020 PFBS). HED = POD ($BMDL_{10}$) / DAF HED = 12.35 mg/kg/d / 317day. HED = 0.0390 mg/kg/d
Uncertainty Extrapolation (USEPA 2018)	
Human Variability (UFH)	10
Animal to Human (UFA)	3
Subchronic to Chronic (UFS)	3 A UFS of 3 is applied because the POD comes from a developmental study of mice. Although this is a susceptible life stage, additional concern over potential hazards following longer-term (chronic) cannot be completely accounted for with this study.
LOAEL to NOAEL (UFL)	1 (BMDL)
Database (UFD)	10 The database lacks studies of chronic duration, neurodevelopment, and immunotoxicity.
Total Composite (UFT)	1000
HED/UFT= Reference Dose (mg/kg-day)	39.0 ng/kg/day (0.000039 mg/kg/d)
Receptor	infant
Ingestion Rate (L/day)	Based on National Health and Nutrition Examination Survey (NHANES) 2005−2010, 95th percentile of water intake for consumers only (direct and indirect consumption) for infants (birth to <1 year old) of 1.106 L/day, per Table 3-17, USEPA Exposure Factors Handbook, 2019.

Body Weight (Kg)	An infant body weight of 7.8 kilograms was used and represents a time-weighted average for birth to 1 year old (Table 8-1, USEPA 2019).
Normalized Drinking Water Intake (L/kg-day)	0.142
Relative Source Contribution	20%
Chronic Non-Cancer MCLG	Chronic Non-Cancer MCLG = RfD x RSC / DWI Chronic Non-Cancer MCLG = 0.055 ug/L or 55 PPT

Table 7: Development of Non-Cancer MCLG for PFBS

10. GenX (HFPO dimer acid and its ammonium salt)

After a literature search and a review of the available evidence and recommendations from various agencies, the DPAG developed an MCLG recommendation for GenX based on Non-Cancer endpoints. US EPA 2018 selected the DuPont oral reproductive/developmental toxicity study in mice as the critical study. (DuPont-18405-1037, 2010). DPAG reviewed this and found it sufficiently robust to provide quality data.

US EPA selected liver effects (single-cell necrosis in male mice) as the critical effect for deriving the subchronic and chronic RfDs for GenX (HFPO dimer acid and its ammonium salt). USEPA (2018) evaluated the relevance of this endpoint in humans and noted that, per Hall, (Hall 2012) liver effects accompanied by effects such as necrosis or inflammation, among others, are indicative of liver tissue damage (USEPA, 2018). This effect is distinct from PPARα-mediated rodent hepatocarcinogenesis. US EPA performed BMD modeling with a BMR of 10%. They reported a $BMDL_{10}$ of 0.15 mg/kg/d based on BMD Multistage 2 model. DAF of 0.15 was developed using allometric scaling, per USEPA (2018 GenX) guidance, since no chemical-specific data on human serum half-life was available that would allow this conversion. Conversely, NCDEQ (NCDDHS 2017) decided against BMD modeling, stating it was statistically unreliable due to poor model fit and large confidence interval. They chose a NOAEL POD and applied a UFT of 1000 to achieve a subsequent RfD at 100 ng/kg/day.

Ultimately, DPAG adopted the approach used by the EPA to develop a HED_{BMDL10}, applied a UFT 300 and produced an RfD of 76.7 ng/kg/day. The ingestion modeling used by NCDEQ to target bottle fed infants was in keeping with the DPAG approach of targeting the most vulnerable populations for protective MCLG. The final MCLG is 108 PPT.

10.a. Review of Critical Study

This study investigated subchronic toxicity of H-28548 (HFPO dimer acid ammonium salt) in Crl:CD1(ICR) mice. Adult male and female mice were administered H-28548 at a dose of 0, 0.1, 0.5, or 5 mg/kg/d by oral gavage with a total of 10 mice per sex per dose for 96 (males) or 97 (females) days. Mice were observed daily for signs of acute toxicity. Body weight, food consumption, and detail the clinical observations were performed weekly. Ophthalmology examination, functional observational battery, and motor activity were evaluated at outset and at the conclusion of the study. Hematology and clinical chemistry studies were performed at study conclusion. Surviving mice were sacrificed and gross and microscopic pathological examinations were performed.

Body weight and body weight gain were increased in the male 5 mg/kg/d dose group relative to control, which was attributed to increased liver weight and not considered an adverse effect. No statistically significant change in body weight or body weight gain were seen any other dose groups. Food consumption and food efficiency were increased in the male 5 mg/kg/d dose group relative to control, which was attributed to increased liver weight and body weight, respectively, and not considered an adverse

effect. No statistically significant change in food consumption or food efficiency were seen any other dose groups.

No acute toxicity or test substance related deaths were seen at any of the doses studied. The test substance had no effect on functional observational battery outcomes at any of the doses studied.

Mean corpuscular hemoglobin (MCHC) was decreased in the male 5 mg/kg/d group relative to controls; because the decrease was minimal (97% of control) and there were no other statistically significant changes in red cell parameters, this outcome was considered to be spurious. Platelet count was increased in males at 0.5 and 5 mg/kg/d, but this did not demonstrate a dose-response relationship, was not associated with clinical signs or pathological changes, and was not seen in a previous 28-day gavage study and was considered to be unrelated to the test substance and not adverse. Absolute monocyte count was decreased in females at 0.1 mg/kg/d. However, similar changes were not demonstrated in the higher dose groups and this effect was considered to be not test substance related or adverse.

AST, ALT, sorbitol dehydrogenase, alkaline phosphatase and total bile acids were increased in the male 5 mg/kg/d group as compared to controls. ALT, sorbitol dehydrogenase, and alkaline phosphatase were increased in the female 5 mg/kg/d group as compared to controls. Changes in these parameters correlated with hepatocellular damage and/or cholestasis and were considered to be adverse effects related to the test substance. Significant differences in liver function parameters were not seen at the lower test doses. Total protein and albumin were increased, and total cholesterol was decreased in male mice at the 5 mg/kg/d dose, however the magnitude

of change was small, was considered to be related to the test substance but non-adverse in nature. Albumin was increased and bilirubin was decreased in the female 5 mg/kg/d group, however the magnitude of change was small and was considered to be non-adverse. Decreased Billy Rubin was also seen in male mice at the 0.5 mg/kg/d dose, but this finding was not replicated at higher doses and was considered to be spurious.

Serum potassium was decreased in male and female mice at the 5 mg/kg/d dose. The changes were not associated with any clinical signs of hypokalemia and this finding was considered to be non-adverse. Chloride was higher in male mice at the 5 mg/kg/d dose, which was considered to be unrelated to the test substance and non-adverse.

Absolute and relative liver weight were increased in male mice at the 0.5 and 5 mg/kg/d those groups relative to control, with a dose response relationship. Absolute and relative liver weight were increased in female mice at the 5 mg/kg/d dose group only. These changes were associated with gross and microscopic pathology findings and were considered to be treatment related.

Relative kidney weight as compared to brain was increased in males at the 5 mg/kg/d dose group; however, absolute and relative kidney weight as compared to body were unchanged and this finding therefore was considered to be of uncertain significance. Relative brain and epididymis weight were lower and relative heart weight as compared to brain was higher in males at the 5 mg/kg/d dose; however, absolute changes in the organ weights were not significant and these findings were not associated with any microscopic pathology findings and were considered to be not related to the test substance. Relative spleen weight was decreased in females at the

0.5 and 5 mg/kg/d dose groups; however, there was no dose response relationship or findings on microscopic pathology examination and these findings were therefore considered spurious and unrelated to the test substance. Absolute and relative ovary weight were increased in females at the 0.5 mg/kg/d dose; however, there was no dose response relationship, the increased ovary weight was attributed to ovarian cysts present in three female mice in that dose group, and this finding was therefore considered spurious and unrelated to the test substance.

There was a significant increase in enlarged and discolored livers in males at the 0.5 and 5 mg/kg/d dose group and in females at the 5 mg/kg/d dose group as compared to controls. These findings were considered to be related to the test substance. There were no other findings on gross pathology examination that were considered to be related to the test substance.

On microscopic examination, hepatocellular hypertrophy without liver cell injury was seen in male mice at the 0.5 mg/kg/d dose, which was considered to be treatment related but not adverse. Hepatocellular hypertrophy, hepatocellular single cell necrosis, and increased pigment concentration in Kupffer cells were seen in both male and and female mice at the 5 mg/kg/d dose. An increased number of mitotic figures were seen in male but not female mice at the same dose. Incidences and severity of liver changes were greater in males as compared to females. These changes correlated with clinical chemistry effects and were considered to be both treatment related and adverse effects. Minimal renal tubular epithelial hypertrophy was seen in male mice at the 5 mg/kg/d dose, but this was not associated with renal tubular cell degeneration or necrosis or any

change in clinical chemistry parameters and was therefore considered to be non-adverse. No other microscopic observations were considered to be treatment related.

An additional pharmacokinetic study was performed in which male and female adult mice were administered the same H-28548 doses at 5 mice per sex dose per timepoint and evaluated for plasma concentration of the test substance approximately two hours after dosing on test days 0, 28, and 95. These mice were also evaluated for bodyweight, food consumption, and clinical signs of overt toxicity but did not have the ophthalmology (postexposure), neurobehavioral, hematology, clinical chemistry, or pathology examinations. Test substance concentration in blood was similar on days 0, 28, and 95 and female mice indicating rapid clearance of the substance from the blood and steady state concentrations achieved on the first day of dosing. In male mice, steady state concentration was achieved by day 28.

10.b. Development of MCLG

DAPG adopted the USEPA performed BMD modeling with a BMR of 10% and a reported $BMDL_{10}$ of 0.15 mg/kg/d based on BMD Multistage 2 model. A DAF of 0.15 was developed using allometric scaling, per USEPA (2018 GenX) guidance, since no chemical-specific data on human serum half-life was available that would allow this conversion. DPAG adopted the approach used by the EPA to develop a HED_{BMDL10}, applied a UFT 300 and produced an RfD of 76.7 ng/kg/day. The ingestion modeling used by NCDHHS (2017) to target bottle fed infants was in keeping the DPAG approach of targeting the most vulnerable populations for protective MCLG (Table 8). The final MCLG is 108 PPT.

GenX	
Method of Administered Dose conversion to Internal Serum Level	BMR 10% $BMDL_{10}$ of 0.15 mg/kg/d based on BMD Multistage 2 model developed by USEPA (2018 GenX)
Method to Derive Human Equivalent Dose	Allometric DAF = $(BWA^{1/4}/BWH^{1/4})$
Dose Response Modeling Method	$BMDL_{10}$ from USEPA (2018 GenX)
HED_{BMDL10} = POD x DAF	DAF = $(BWA^{1/4}/BWH^{1/4})$ DAF = $(0.0372\ kg)^{1/4}/(80\ kg)^{1/4}$ DAF = 0.15 HED_{BMDL10} = POD ($BMDL_{10}$) x DAF HED_{BMDL10} = 0.15mg/kg/d x 0.15 HED_{BMDL10} = 0.0225 mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	10
Animal to Human (UFA)	3
Subchronic to Chronic (UFS)	3
LOAEL to NOAEL (UFL)	1 (BMDL)
Database (UFD)	3 (insufficient number of studies)
Total Composite (UFT)	300
RfD = HED/UFT (mg/kg/d)	76.7 ng/kg/day (76.7 x10-6 mg/kg/d)
Receptor	Bottle fed infant
Ingestion Rate (L/day)	Based on National Health and Nutrition Examination Survey (NHANES) 2005−2010, 95th percentile of water intake for consumers only (direct and indirect consumption) for infants (birth to <1 year old) of 1.106 L/day, per Table 3-17, USEPA Exposure Factors Handbook, 2019.
Body Weight BW (Kg)	An infant body weight of 7.8 kilograms was used and represents a time-weighted average for birth to 1 year old (Table 8-1, USEPA 2019).

Normalized Drinking Water Intake (NDWI) (L/kg-day)	0.142
Relative Source Contribution (RSC)	20%
MCLG	MCLG = RfD x RSC / NDWI MCLG = 0.108 ug/L or 108 PPT

Table 8: Development of Non-Cancer MCLG for GenX

11. Summary

The DPAG had the opportunity to build on the diligent work of a great number of US and State agencies who preceded us. We strove to find the best practices wherever possible and apply them in a scientifically valid and data driven manner. As new information becomes available, we would welcome the opportunity to review these MCLG recommendations and modify when appropriate. The summary of recommendations are as follows:

1. These proposed Non-Cancer MCLGs are suggested with the health of the most vulnerable populations in mind
2. Individual MCLGs are advisable and the most scientifically rigorous approach
3. Non-Cancer MCLGs are low enough to protect against Cancer endpoints

PFAS	Reference Dose	MCLG proposed
perfluorooctanoic acid (PFOA)	3.9 ng/kg/day	8 PPT
perfluorooctanesulfonic acid (PFOS)	3.1 ng/kg/day	14 PPT
perfluorononanoic acid (PFNA)	2.2 ng/kg/day	6 PPT
perfluorohexanesulfonic acid (PFHxS)	4.0 ng/kg/day	20 PPT
perfluoroheptanoic acid (PFHpA)	None derived	8 PPT
perfluorobutanesulfonic acid (PFBS)	39 ng/kg/day	55 PPT
ammonium salt of hexafluoropropylene oxide dimer (GenX)	75 ng/kg/day	108 PPT

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Appendix A: Drexel PFAS Advisory Group (DPAG)

Drexel PFAS Advisory Group (DPAG) adhered an evidence-based approach in developing its proposal. (Institute of Medicine (2011), NRC (2009)) The process was transparent and reviewed by PADEP at regular intervals. No member disclosed a conflict of interest. The panel was multidisciplinary and included a wide array of expertise. Literature and scientific evidence were reviewed with a systematic approach that rated the quality of the evidence, grade the strength of recommendations, incorporate values and preferences, and acknowledge differences in opinion. Recommendations were articulated in a structured framework repeatable across each PFA examined. They are now submitted for external review by DEP.

Project Leader and Medical Toxicologist:

- Richard J Hamilton MD FAAEM, FACEP, FACMT. Professor and Chair, Emergency Medicine, Drexel University College of Medicine. Board Certified in Medical Toxicology by the American Board of Emergency Medicine and is a Fellow of the American College of Medical Toxicology.

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- Rita McKeever MD FAAEM, FACMT, Associate Professor of Emergency Medicine, Drexel University College of Medicine. Board Certified in Medical

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Expert Panel:

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- Christopher Sales Ph.D. Assistant Professor, Architectural & Environmental Engineering, Drexel University
- Marie Kurtz PhD, Senior Scientist; Assistant Research Professor, Academy of Natural Sciences, Drexel University
- Esther D. Chernak, MD, MPH Associate Clinical Professor, Drexel University College of Medicine and Dornsife School of Public Health
- Tom Hipper, MSPH, MA Adjunct Professor, Program Manager of the Center for Public Health Readiness and Communication Dornsife School of Public Health, Drexel University

Appendix B: Acronyms and Abbreviations List

ATSDR: Agency for Toxic Substances and Disease Registry
BMD: benchmark dose
BMDL: lower confidence limit on the benchmark dose
BMR: benchmark response
BW: body weight
Bwa: body weight animal
BWh: body weight human
CDC: Centers for Disease Control and Prevention
CEPA: California Environmental Protection Agency
DPAG: Drexel PFAS Advisory Group
DAF: dosimetric adjustment factor
GD: gestational day
GenX: ammonium salt of hexafluoropropylene oxide dimer
HBV: health-based value
HED: human equivalent dose
$HED_{LOAEL:}$ HED determined by LOAEL
$HED_{BMDL10:}$ HED determined by a BMR of 10%
$HED_{BMDL0.5SD:}$ HED determined by a BMR of 50% of SD
HFPO: hexafluoropropylene oxide
HRA: health risk assessment
THSV = Internal Target Human Serum Value
kg: kilogram
L: liter
LD: lactation day
LHA: lifetime health advisory
LOAEL: lowest observed adverse effect level
MCL: Maximum Contaminant Level
MDH: Minnesota Department of Health
MDHHS: Michigan Department of Health and Human Services
mg: milligram
mg/kg/d: milligrams per kilogram per day
MI: Michigan
ml: milliliter
MPART: Michigan PFAS Action Response Team
NCDHHS: North Carolina Department of Health and Human Services
NHDES: New Hampshire Department of Environmental Services
NHANES: National Health and Nutrition Examination Survey
NJDEP: New Jersey Department of Environmental Protection
ng: nanogram
NOAEL: no observed adverse effect level
OECD: Organization for Economic Co-operation and Development
PA DEP: Pennsylvania Department of Environmental Protection
PFAS: per- and polyfluoroalkyl substances
PFBS: perfluorobutane sulfonic acid
PFHpA : perfluoroheptanoic acid
PFHxA: perfluorohexanoic acid
PFHxS: perfluorohexane sulfonic acid
PFNA: perfluorononanoic acid
PFOA: perfluorooctanoic acid
PFOS: perfluorooctane sulfonic acid
PND: postnatal day
POD: point of departure
PODHED: point of departure human equivalent dose
PPAR: peroxisome proliferator-activated receptor
ppt: parts per trillion
RfD: reference dose
RSC: relative source contribution
TWA: time weighted average
UF: uncertainty factor
µg: microgram
USEPA: United States Environmental Protection Agency