Fact Sheet Date: April 8, 2021

NEW YORK STATE HUMAN HEALTH FACT SHEET¹

Ambient Water Quality Value for Protection of Human Health and Sources of Potable Water

SUBSTANCE: Perfluorooctanoic Acid (PFOA)

CAS REGISTRY NUMBER: 335-67-1



AMBIENT WATER QUALITY VALUE: 0.0067 mcg/L

BASIS: Oncogenic Effects (6 NYCRR 702.4)

INTRODUCTION

Perfluorooctanoic acid (PFOA, C8, or perfluorooctanoate) is an environmentally persistent anthropogenic chemical that is primarily used as a reactive intermediate in the production of PFOA salts, which are used as processing aids in the production of fluoropolymers and fluoroelastomers (HSDB, 2016; US EPA, 2016a). PFOA has also been used in fire-fighting foams, cosmetics, greases, lubricants, paints, polishes and adhesives, which contribute to its release into the environment through various waste streams (HSDB, 2016). PFOA is also released into the environment from fluoropolymer manufacturing or processing facilities, effluent releases from wastewater treatment plants, landfill leachates and from degradation/transformation of PFOA precursors (EC/HC, 2012).

The toxicity of PFOA and its salts (e.g., ammonium perfluorooctanoate (APFO)²) has been reviewed and summarized by authoritative bodies (ATSDR, 2018; EC/HC, 2012; NJ DEP, 2007, 2019; NJ DWQI, 2017; NJ DEP, 2019; US EPA, 2005a, 2006, 2014, 2016a). These summaries identify important studies on the health effects associated with exposure to PFOA and its salts, including studies on the chronic (oncogenic and nononcogenic), developmental, and reproductive effects observed in humans and animals (when available). We derived the ambient water quality value of 0.0067 mcg/L for PFOA using available toxicological data and risk assessments, the definitions in 6 NYCRR 700.1, and the procedures outlined in 6 NYCRR 702.2 through 702.7.

¹ A list of commonly used abbreviations and acronyms is attached as Exhibit 4.

² Most of the toxicology studies have been conducted with APFO (CASRN: 3825-26-1), the ammonium salt of PFOA, which has a slightly higher molecular weight (431.1) than PFOA (414.07). However, most of the toxicological literature and risk assessments consider the PFOA doses to be equivalent to the experimental APFO doses, which we will do herein.

702.3. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON SPECIFIC MCLS AND PRINCIPAL ORGANIC CONTAMINANT CLASSES

PFOA has a Specific MCL of 0.01 mcg/L as defined in 6 NYCRR 700.1. Thus, the potential ambient water quality value for PFOA under 6 NYCRR 702.3 is 0.01 mcg/L.

702.4. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON ONCOGENIC EFFECTS

There is limited information available on the oncogenic potential of PFOA in humans. The two key studies that show evidence of positive associations between PFOA serum levels and risks of kidney and testicular cancer in humans are of highly-exposed communities within the Ohio River Valley (Barry et al. 2013; Vieira et al., 2013). IARC (2016) summarized these two studies (shown below), along with two other studies that evaluated PFOA exposure and the potential for increased cancer risk in occupationally exposed industrial workers (Steenland and Woskie, 2012; Raleigh et al., 2014).

[&]quot;5.2.1 Cancer of the testis

The only informative results on risk of cancer of the testis were from two studies of cancer incidence in a high-exposure community setting in West Virginia and Ohio, USA; there was some overlap in the cases examined in these studies. Both publications, using different study designs (i.e. a cohort study of incidence and a population-registry case–control study), observed an increased risk of incidence of cancer of the testis. In the highest quartile of exposure in both studies, the observed increase in risk was approximately threefold, with a significant trend in increasing risk with increasing exposure in the cohort study (no trend test was reported in the case–control study). The evidence for cancer of the testis was considered credible and unlikely to be explained by bias and confounding, however, the estimate was based on small numbers."

[&]quot;5.2.2 Cancer of the kidney

There were several publications that have examined PFOA and risk of cancer of the kidney. Three of these were conducted in West Virginia, USA, and included occupational and community exposure, and the fourth was conducted in a different occupational setting. In the exposure–response analysis of workers in West Virginia, 8 of the 12 deaths from cancer of the kidney were seen in the highest quartile of exposure, with an elevated standardized mortality ratio and a significant trend in increasing risk with increasing exposure. The other occupational cohort study reported no evidence for increased incidence. A modestly increased risk of incidence of cancer of the kidney was seen in a community population with high exposure. A study in a somewhat overlapping population also found elevated relative risks in the groups with high and very high exposure compared with the group with low exposure. The evidence for cancer of the kidney was considered credible; however, chance, bias, and confounding could not be ruled out with reasonable confidence."

Studies in laboratory animals provide additional evidence for the oncogenicity of PFOA. In a two-year dietary study of Sprague-Dawley rats exposed to APFO (0, 1.3, or 14.2 mg/kg-day), statistically significant, dose-related increased incidences of Leydig cell tumors in males (also called testicular interstitial cell tumors) and mammary fibroadenomas in females were observed (Butenhoff et al., 2012). In a single-dose two-year dietary study, APFO (13.6 mg/kg-day) induced Leydig cell tumors, liver adenomas, and pancreatic acinar cell tumors in male Sprague-Dawley rats (Biegel et al., 2001). Based on the available evidence of oncogenicity in studies of humans and laboratory animals, IARC (2016) classifies PFOA as *possibly carcinogenic to humans (Group 2B)* and the US EPA (2016a) classifies PFOA as having *suggestive evidence* for carcinogenicity.

PFOA induces tumors at multiple sites in rats (i.e., liver, mammary gland, testicular Leydig cell, and pancreatic acinar cell tumors) and has oncogenic effects under 6 NYCRR 700.1(a)(39)(iii), based on induction of tumors in one mammalian species, reported in two independent studies. The low background tumor rates observed at some tumor sites provides additional support for concluding that PFOA has oncogenic effects. For example, the incidence of Leydig cell tumors in control male rats [in both the Biegel et al. (2001) and Butenhoff et al. (2012) studies] and pancreatic acinar cell tumors (Biegel et al., 2001) was 0%.

Short-term *in vitro* assays of PFOA in bacteria and mammalian cells and *in vivo* studies of rats and mice showed mixed results, but overall, results indicate that PFOA is not mutagenic (EC/HC, 2012; IARC, 2016; US EPA, 2016a). It has been hypothesized that PFOA may induce liver tumors via a nongenotoxic MOA involving activation of peroxisome proliferator-activated receptors (PPAR)³ (US EPA, 2005a, 2006, 2016a). However, the specific MOA for the oncogenicity of PFOA is unknown^{4,5}(NJ DWQI, 2017; NJ DEP, 2019; US EPA, 2006, 2016a). Therefore, under 6 NYCRR 702.4, "the standard or guidance value shall be based on the 95 percent lower confidence limit on the human dose corresponding to an excess lifetime cancer risk of one-in-one million."

³ PPAR-alpha is one of three members, along with PPAR-delta and PPAR-gamma, of the subfamily of PPARs.

⁴ PFOA induces a "tumor triad" (i.e., liver, Leydig cell tumors, and pancreatic acinar cell tumors), which is characteristic of PPARalpha agonists (US EPA, 2005a). In its review of the US EPA's "Draft Risk Assessment of Potential Human Health Effects Associated with Perfluorooctanoic Acid (PFOA) and Its Salts" (US EPA, 2005a), the majority of the Scientific Advisory Board (SAB) expert panel concluded that there is insufficient evidence to support a conclusion that PPAR-alpha is the sole MOA for liver tumors or to determine the carcinogenic MOA for Leydig cell tumors, pancreatic acinar cell tumors, and mammary gland tumors (US EPA, 2006).

⁵ US EPA (2005b) guidance recommends the use of age-dependent adjustment factors (ADAFs) when assessing the cancer risks of chemicals that act through a mutagenic mode of action (MOA) for carcinogenicity. Given that the oncogenic MOA for PFOA is unknown, and the available data do not suggest that PFOA acts through a mutagenic MOA, ADAFs were not used in the derivation of potential ambient water quality values for PFOA (oncogenic effects).

Human epidemiological studies (as described above) provide supporting evidence of the carcinogenicity of PFOA but are too limited for use in a quantitative dose-response assessment (NJ DWQI, 2017; NJ DEP, 2019). Cancer potency estimates based on dose-response assessment of data from human epidemiological studies are not available. Three cancer potency estimates are available for PFOA that are based on linear low-dose extrapolation (NJ DWQI, 2017; NJ DEP, 2019; US EPA, 2016; Tardiff et al., 2009)⁶, and from which human doses corresponding to one-in-one million excess lifetime cancer risks (at 95 percent lower confidence limits) can be calculated.⁷ All three cancer potency estimates are based on benchmark dose modeling of Leydig cell tumor incidence (Table 1) reported in the multiple-dose dietary study in male rats (Butenhoff et al., 2012; Sibinski, 1987). The New Jersey Department of Environmental Protection (NJ DEP) (NJ DWQI, 2017; NJ DEP, 2019) and the US EPA (2016a) cancer potency estimates are based on administered dose PODs and Tardiff et al. (2009) used pharmacokinetic modeling to estimate an internal dose POD (i.e., estimated PFOA concentrations in blood plasma).

The US EPA (2016a) calculated a CPF of 0.07 per mg/kg-day for PFOA and derived a water concentration at the one-in-one million excess lifetime cancer risk level of 0.457 mcg/L. Using the Leydig cell tumor data in male rats (Table 1) from Butenhoff et al. (2012), the US EPA calculated a BMDL₀₄ of 1.99 mg/kgday. The US EPA used a default allometric scaling approach (i.e., BW^{3/4} scaling) (Table 2) to calculate an HED (0.58 mg/kg-day) and used linear extrapolation to calculate a human dose corresponding to a one-in-one million (lower 95% confidence limit) excess lifetime cancer risk (1.4×10^{-5} mg/kg-day). These methods (including the use of the multistage cancer model and the default allometric scaling approach for interspecies extrapolation) are consistent with the procedures outlined in 6 NYCRR 702.4. However, the water concentration at the one-inone million cancer risk level derived by the US EPA (2016a) assumes an 80-kg adult consumes 2.5 liters of water per day. Using exposure factors that are consistent with NYCRR 702.2 and 702.4 (i.e., assuming a 70-kg adult consumes 2 liters of water per day) and the human dose at the one-in-one million cancer risk level estimated by the US EPA (1.4×10^{-5} mg/kg-day), we calculated a potential ambient water quality value (oncogenic effects) of 0.49 mcg/L based on the US EPA (2016a) cancer potency factor. While use of default allometric scaling to calculate an HED is consistent with NYCRR 702.4, it should be noted that its use to derive a cancer potency value for PFOA is not a preferred interspecies extrapolation method as it does not adequately

⁶ The cancer potency estimate and reference dose derived by NJ DEP (2019) is also documented in an earlier report from the NJ Drinking Water Quality Institute (i.e., NJ DWQI, 2017).

⁷Health Canada (2018) evaluated the oncogenic effects of PFOA and derived a tolerable daily intake (or reference dose) based on the increased incidence of Leydig cell tumors in male rats. However, under 6 NYCRR 702.4, the human equivalent dose for oncogenic effects shall be based on the use of linear low dose extrapolation when the oncogenic MOA of a chemical is not known. Therefore, Health Canada's tolerable daily intake was not further considered as a potential basis for an ambient water quality value for PFOA based on oncogenic effects.

adjust for the large pharmacokinetic differences in PFOA serum clearance between animals and humans, and as a result, could potentially underestimate cancer risks at the human equivalent oral dose. Studies of oral PFOA exposure in experimental animals indicate serum half-lives of approximately 17 to 19 days in mice, 21 to 33 days in cynomolgus monkeys, and 0.12 to 8.4 days (2.8 to 202 hours) in rats (Tardiff et al., 2009; US EPA, 2005a, 2009). Most studies that have evaluated PFOA clearance in humans longitudinally report human halflives within a range of 2 to 4 years (central tendency estimates) (Li et al., 2018; Health Canada, 2018; US EPA, 2016a). Therefore, a daily ingested dose in humans would result in a higher internal dose (at near steady-state) than the same daily ingested dose in experimental animals (NJ DWQI, 2017; NJ DEP, 2019).

The NJ DEP (NJ DWQI, 2017; NJ DEP, 2019) derived a cancer-based drinking-water concentration (0.014 mcg/L) for PFOA based on a BMDL₀₅ of 2.36 mg/kg-day, which is also based on Leydig cell tumors in male rats (Butenhoff et al., 2012). Using the BMDL₀₅, the NJ DEP calculated a CPF of 0.021 per mg/kg-day in rats and estimated the animal dose corresponding to a 95% LCL on a one-in-one million excess lifetime cancer risk (4.8 x 10^{-5} mg/kg-day). The NJ DEP applied a chemical-specific pharmacokinetic adjustment factor (Table 2) to calculate a human equivalent dose of 4 x 10^{-7} mg/kg-day (which corresponds to a human CPF of 2.5 per mg/kg-day). The methods used in the NJ DEP's derivation (including the choice of dose-response models, use of a chemical-specific approach for interspecies extrapolation, and the selected exposure assumptions) are consistent with the procedures outlined in 6 NYCRR 702.2 and 702.4. Under 6 NYCRR 702.4, allometric scaling (i.e., BW^{3/4} scaling) is the primary method for calculating HEDs from cancer PODs in laboratory animals. However, 6 NYCRR 702.4 also allows for use of alternative methods for calculating HEDs when "deemed more appropriate based on scientific evidence." Using an alternative (chemical-specific) method for extrapolating from an animal POD to an HED is more appropriate for PFOA given the large differences in serum clearance of PFOA between animals and humans.

Tardiff et al. (2009) evaluated PFOA cancer data and calculated an internal dose POD based on the same Leydig cell tumor incidence data in rats (Table 1) as used by the US EPA (2016) and NJ DEP (NJ DWQI, 2017; NJ DEP, 2019) (initially reported in an unpublished industry report Sibinski (1987) and later published in Buttenhoff et al., 2012). Tardiff et al. (2009) used an internal dose (i.e., PFOA plasma concentration) for determining PFOA's cancer potency because PFOA blood concentrations are a more appropriate metric for evaluating systemic effects than administered (i.e., ingested) dose due to the large differences in the serum halflives of PFOA in animals and humans.

Tardiff et al. (2009) calculated internal plasma PFOA concentrations in rats from administered PFOA

doses (0, 1.3, and 14.2 mg/kg-day) using a rat PBPK model (reported in Tan et al., 2008). The authors then estimated, using the cancer multistage model, the 95% LCL on PFOA concentration in plasma associated with a 10% tumor incidence rate in rats (i.e., a LBMIC₁₀⁸ of 203 micrograms per milliliter (mcg/mL)). We did not consider the use of alternate models because the multistage model adequately described the data within the range of observation.⁹ This approach is permitted under 6 NYCRR 702.4, and is consistent with the US EPA cancer risk-assessment guidance and practice giving preference (among models that adequately described the data) to the multistage model when modeling cancer bioassay data¹⁰ (Gehlhaus et al., 2011; US EPA, 2012a,b).

In Tardiff et al. (2009), human equivalent doses were calculated from internal dose PODs in rats (i.e., PFOA plasma concentrations) using an unpublished human PBPK model (cited in Tardiff et al. (2009) as Clewell (2006)). Generally, a multicompartment PBPK-based approach would be more preferred than a single compartment pharmacokinetic method for extrapolating between animals and humans. However, given the absence of available documentation on the unpublished human PBPK model (Clewell, 2006) used to calculate the HED from plasma PFOA concentrations in animals in the Tardiff et al. (2009) analysis, we used a single-compartment pharmacokinetic approach to calculate an HED from the LBMIC₁₀. Similar single-compartment pharmacokinetic approaches have been used by other authoritative bodies (US EPA, 2016a; NJ DWQI, 2017; NJ DEP, 2019) to address the large pharmacokinetic differences in PFOA serum clearance between animals and humans. According to Tardiff et al. (2009), the following parameters were taken into consideration in the calculation of the human PBPK-based adjustment factor (0.127): "body weight, cardiac output, volume of renal filtration rate, volume of distribution, half-life (3.5 years; Olsen et al., 2007), transport affinity, transfer rate constant, and free fraction in plasma." The human half-life of 3.5 years (geometric mean) is based on serum measurements in an occupational cohort followed over a 5 year period (Olsen et al., 2007), and is within the range of human half-lives reported in studies with longitudinal serum measurements of communities

⁸ The 95% LCL of Bench-Mark Internal Concentration for a 10% response above background (Butenhoff et al., 2004; Tardiff et al., 2009). The LBMIC is a lower-bound benchmark dose (i.e., BMDL₁₀) PFOA serum concentration and is analogous to an LED, which is the 95 percent lower confidence limit on the effective dose as described in 6 NYCRR 702.4.

⁹ Tardiff et al. (2009) used goodness-of-fit as a criterion to determine the suitability of benchmark dose models for use in deriving the BMD, and BMDL.

¹⁰ The US EPA (2012a) noted, "in the absence of a biologically based model, dose-response modeling is largely a curve-fitting exercise among the variety of available empirical models. Currently there is no recommended hierarchy of models that would expedite model selection, in part because of the many different types of datasets and study designs affecting dose-response patterns. As more flexible models are developed, hierarchies for some categories of endpoints will likely be more feasible. Some model hierarchies could be established as preferred practices. For example, it is a current practice of US EPA's IRIS program to prefer the multistage model for cancer dose-response modeling of cancer bioassay data (Gehlhaus et al., 2011). The multistage model (in fact a family of different stage polynomial models) is sufficiently flexible for most cancer bioassay data, and its use provides consistency across cancer dose-response analyses." More specifically, to support using only the multistage model to determine the carcinogenic potency of tetrachloroethene, US EPA (2012b) noted, "The multistage model has been used by EPA in the majority of quantitative cancer assessments, initially because of its parallelism to the multistage carcinogenic process. A benefit of the multistage model is its flexibility in fitting a broad array of dose-response patterns, including allowing linearity at low dose."

environmentally exposed to PFOA (i.e., 2.3 years (Bartell et al., 2010), 2.7 years (Li et al., 2018), 3.26 years (Brede et al., 2010), and 3.9 years (Worley et al., 2017)). In addition, authoritative bodies have based singlecompartment pharmacokinetic models for PFOA on human half-lives of 2.3 or 3.8 years (US EPA, 2016a; NJ DWQI, 2017; NJ DEP, 2019; ATSDR, 2018). Thus, the half-life of 3.5 years from the Olsen et al. (2007) study is within the appropriate range for estimating human serum clearance of PFOA and support for use of this half-life estimate is strengthened by the individual-level serum analysis and comparatively long follow-up period of about 5 years. Using the same human half-life estimate (3.5 years) as was used to estimate the pharmacokinetic adjustment factor cited in Tardiff et al., 2009 (based on the Clewell (2006) human PBPK model), and the PFOA volume of distribution for humans from the US EPA (2016a), we calculated a serum clearance factor of 0.092 mL/kg-day using the equation shown below.

PKAF = estimated PFOA serum clearance (CL) in humans

CL = Volume of distribution x (ln 2 \div human PFOA serum ¹/₂ life estimate)

= 0.17 L/kg x (0.693 / 1277.5 days)

 $= 9.2 \text{ x } 10^{-5} \text{ L/kg-day} (0.092 \text{ mL/kg-day})$

Where,

Volume of distribution = 0.17 L/kg (US EPA, 2016a)

 $\ln 2 = 0.693$

PFOA serum half-life in humans = $(3.5 \text{ years } \times 365 \text{ days/year} = 1277.5 \text{ days})$

Using the PKAF calculated above, we estimated a human equivalent dose at the LBMIC₁₀ (i.e., $HED_{LBMIC10}$) from Tardiff et al. (2009).

 $HED_{LBMIC10} = LBMIC_{10} x PKAF x PDAF$

where,

LBMIC₁₀ = 203 mcg/mL_{PLASMA} PKAF = Pharmacokinetic Adjustment Factor = 0.092 mL/kg-day PDAF = Pharmacodynamic Adjustment Factor = 1

 $\text{HED}_{\text{LBMIC10}} = 203 \text{ mcg/mL}_{\text{PLASMA}} \times 0.092 \text{ mL/kg-day} \times 1$

 $\text{HED}_{\text{LBMIC10}} = 19 \text{ mcg/kg-day}$

We divided the HED_{LBMIC10} by 100,000 to obtain the human dose ($1.9 \times 10^{-4} \text{ mcg/kg-day}$) corresponding to the 95% LCL on the dose associated with an excess lifetime human cancer risk of one-in-one-million.¹¹ Then, using methods consistent with 6 NYCRR 702.2 and 702.4, we calculated the PFOA water concentration (0.0067 mcg/L, two significant figures) associated with an excess lifetime cancer risk of one-in-one million using the risk-specific (1×10^{-6}) dose ($1.9 \times 10^{-4} \text{ mcg/kg-day}$) and assuming a 70-kg adult consumes 2 liters of water per day over a lifetime exposure period of 70 years.

Risk-Specific (1 x 10⁻⁶) Water
ConcentrationRisk Specific (1 x 10⁻⁶) Dose x Body Weight1 x 10⁻⁶ Water Concentration= $\frac{1.9 x 10^{-4} mcg/kg-day x 70 kg}{2 L/day}$ 1 x 10⁻⁶ Water Concentration=0.0067 mcg/L

The water concentration of 0.0067 mcg/L is selected as the potential ambient water quality guidance value (oncogenic effects) for PFOA as it is more stringent than values based on the NJ DEP and US EPA derivations (0.014 mcg/L and 0.49 mcg/L, respectively), as well as the potential ambient water quality value (0.0091 mcg/L) based on the use of the LBMIC₁₀ and the pharmacokinetic adjustment factor (based on Clewell (2006) reported in Tardiff et al. (2009)). Selection of the ambient water quality value of 0.0067 mcg/L is also strengthened by use of a PBPK model to estimate plasma PFOA concentrations in rats from applied doses for use in estimating a POD (Tardiff et al., 2009). Moreover, use of a chemical-specific approach for extrapolating from animals to humans, as was used in this derivation, is preferred (i.e., "deemed more appropriate") under 6 NYCRR 702.4 than use of allometric scaling (i.e., BW^{3/4} scaling) given the large pharmacokinetic differences between animals and humans.

702.5. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON

¹¹ A dose at any lifetime excess cancer risk can be obtained from the straight line that extrapolates 10% excess lifetime cancer risk at the HED_{LBMIC10} to zero excess risk at zero dose. For example, a one-in-one-million excess lifetime risk (equal to 0.000001) is 100,000-fold lower than an excess lifetime risk of 10% (equal to 0.1). Therefore, the dose at a one-in-one-million excess lifetime risk is obtained by dividing the dose at a 10% excess risk by 100,000 (equal to 0.1/0.000001).

NONONCOGENIC EFFECTS

Studies of human exposure to PFOA have reported positive associations between PFOA serum levels and nononcogenic health effects (e.g., kidney effects, ulcerative colitis, thyroid effects, and pregnancy-induced hypertension) among workers and/or community residents in the Ohio River valley (C8 SP, 2017; Darrow et al., 2013; Steenland et al., 2012, 2013; Winquist, Steenland, 2014). Numerous additional epidemiology studies of PFOA exposure in the general population and/or other worker cohorts have been conducted (ATSDR, 2018; US EPA, 2016a). However, these studies in humans do not have adequate quantitative information on the dose and duration of human exposures that correspond to human serum PFOA levels (US EPA, 2016a), and therefore are generally not used for quantitative risk assessment.

Using health effects information from animal studies, the US EPA (2016a,b), the Minnesota Department of Health (MDH, 2018) and the NJDEP (NJ DWQI, 2017; NJ DEP, 2019) derived reference doses (RfDs) and health-based values for PFOA in drinking water. Each of these agencies used nononcogenic points of departure based on internal doses (i.e., serum concentrations of PFOA) to address differences in PFOA half-life between animals and humans (Table 3).

The US EPA (2016a,b) based its RfD on developmental toxicity (reduced ossification at birth and accelerated time to puberty) in the offspring of mice exposed to APFO during days 1 to 17 of gestation (Lau et al., 2006; see Exhibit 1). The US EPA converted the LOEL of 1 mg/kg-day to a serum PFOA level (38 mg/L) using the rodent pharmacokinetic model of Wambaugh et al. (2013), and then used a human one-compartment pharmacokinetic model to obtain the corresponding human point of departure (LOEL_{HED} = 0.0053 mg/kg-day).¹² Application of a total uncertainty factor of 300 (10X each for intraspecies differences and use of a LOEL, and 3X for interspecies differences in pharmacodynamics) yielded the RfD of 2.0 x 10⁻⁵ mg/kg-day.

The MDH (2018) derived a numerically identical RfD ($2 \times 10^{-5} \text{ mg/kg-day}$) for PFOA using the same toxicological endpoint and human point of departure (see Exhibit 2). Their total uncertainty factor was the same as the US EPA's (300X), but the MDH applied a lower uncertainty factor for use of a LOEL (3X instead of 10X), and added an uncertainty factor for database incompleteness (3X).

The NJ DEP (NJ DWQI, 2017; NJ DEP, 2019) derived an RfD (2 x 10⁻⁶ mg/kg-day) based on liver

¹² Human equivalent dose (HED_{LOEL}) = PFOA serum concentration x PFOA clearance = 38 mg/L x 0.00014 L/kg-day = 0.0053 mg/kg/day. PFOA clearance = $(\ln 2/\text{PFOA half-life}) \text{ x volume of distribution} = (0.693/839.5 \text{ days}) \text{ x } 0.17 \text{ L/kg} = 0.00014 \text{ L/kg-day}$.

toxicity (increased relative liver weights) in adult mice exposed to AFPO for 14 days (Loveless et al., 2006; see Exhibit 3). The measured PFOA serum levels at each dose were used to obtain the lower bound on the modeled serum level for a 10% response (4.35 mg/L, corresponding to an approximate administered dose of 0.13 mg/kg-day), which was used as the point of departure. The NJ DEP applied a total uncertainty factor of 300 (10X each for intraspecies differences and database incompleteness; 3X for interspecies pharmacodynamic differences). The NJ DEP then converted the reference PFOA serum level (0.0145 mg/L) to the RfD using the same PFOA human one-compartment pharmacokinetic model used by the US EPA (2016).¹³

In addition to the assessments from authoritative bodies, we considered other published studies on the health effects of PFOA in animals, and consequently identified a study reporting increased liver weights in the offspring of mice exposed to PFOA during pregnancy (Macon et al., 2011) as an appropriate basis of a potential ambient water quality value for PFOA (nononcogenic effects). The primary considerations in choosing a POD based on this study and toxicological endpoint were:

- Liver toxicity is a well-established and sensitive toxicological endpoint for PFOA in adult and developing animals.
- The LOEL in the study that caused liver effects (0.3 mg/kg-day) is lower than the LOEL that caused developmental toxicity (1 mg/kg-day) in the study used by the US EPA and the MDH.
- Increased liver weights can progress into indicators of liver damage such as histopathological changes and cellular necrosis as the magnitude and duration of PFOA exposure increases.
- The study observed effects in animals at early life stages, which represent a potentially vulnerable window for PFOA toxicity in humans.
- The study measured PFOA serum levels in young animals at the time the effects were observed. This is preferred over the Lau et al. (2006) study, which did not measure serum levels in the offspring that had the developmental effects.

Using methods consistent with 6 NYCRR 702.5, we derived an RfD of 1.5×10^{-6} mg/kg-day (0.0015 mcg/kg-day) for PFOA. We calculated the POD (an HED_{LOEL} of 0.00046 mg/kg-day) from the measured rodent serum PFOA level of 4.98 mg/L at the LOEL using the same human one-compartment model as we used above in the derivation of a CPF from the Tardiff et al. (2009) study.¹⁴ We applied a total UF of 300 (3X for use of a

¹³ Clearance factor is from US EPA (2016). Reference dose = PFOA serum concentration x PFOA clearance = $0.0145 \text{ mg/L x } 0.00014 \text{ L/kg-day} = 2 \text{ x } 10^{-6} \text{ mg/kg-day}$.

¹⁴ Human equivalent dose (HED_{LOEL}) = PFOA serum concentration x PFOA clearance = 4.98 mg/L x 0.000092 L/kg-day = 0.00046 mg/kg/day. PFOA clearance = (ln2/PFOA half-life) x volume of distribution = (0.693/1277.5 days) x 0.17 L/kg = 0.000092 L/kg-

LOEL for mild effects on the liver, 3X for interspecies differences in pharmacodynamics, 10X for inter-human variability, and 3X for database deficiencies) to the HED_{LOEL} to obtain the RfD. The uncertainty factor for database deficiencies is intended to account for limited evidence for effects on the liver and on mammary gland development at PFOA exposures lower than 0.3 mg/kg-day (Macon et al., 2011; Tucker et al., 2015; Quist et al., 2015). The choice of a total UF of 300 is consistent with 6 NYCRR 702.5 given the areas of uncertainty and variation.

$RfD = HED_{LOEL} / UF$

300 (interspecies differences, pharmacodynamics (3X), UF = inter-human variability (10X), use of a LOEL (3X); database incompleteness (3X))

> RfD = 0.00046 mg/kg-day / 300RfD = 1.5 x 10⁻⁶ mg/kg-day or 0.0015 mcg/kg-day

We used this RfD (0.0015 mcg/kg-day) for the derivation of a potential ambient water quality value (nononcogenic effects) for PFOA. We applied the procedure outlined in 6 NYCRR 702.2 and 702.5 to derive a potential ambient water quality value (0.011 mcg/L, rounded to two significant figures) using the selected RfD, allocating 20% (0.2) of the RfD to drinking water, and assuming an adult body weight of 70 kilograms and a drinking-water consumption rate of 2 liters per day.

$$\frac{\text{Potential Ambient Water}}{\text{Quality Value}} = \frac{0.0015 \text{ mcg/kg-day x } 70 \text{ kg x } 0.2}{2 \text{ L/day}} = 0.011 \text{ mcg/L}$$

The use of age-specific drinking-water consumption rates in the derivation to address the potential for children to be more sensitive than adults to the nononcogenic effects of PFOA was considered, but was not used because the weight of scientific evidence is insufficient to conclude that exposure to PFOA during childhood poses a greater risk of nononcogenic effects than exposure during adulthood (ATSDR, 2018; NJ DEP, 2007; Steenland et al., 2010; Tardiff et al., 2009). In addition, for the toxicological endpoint on which the ambient water quality value (nononcogenic effects) is based (increased liver weights), effects were observed at the same PFOA exposure level (0.3 mg/kg-day) in adult mice (Loveless et al., 2006) and in mice exposed gestationally (Macon et al., 2011).

702.7. PROCEDURE FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON CHEMICAL CORRELATION

Chemical-specific toxicological data are sufficient to derive potential ambient water quality values for PFOA based on both its oncogenic (6 NYCRR 702.4) and nononcogenic effects (6 NYCRR 702.5). Thus, values based on oncogenic or nononcogenic effects using chemical correlation are unnecessary.

SELECTION OF VALUE

According to 6 NYCRR 702.2(b), the ambient water quality value [Health (Water Source)] shall be the most stringent of the potential values derived using the procedures found in 6 NYCRR 702.3 through 702.7. Using procedures from 6 NYCRR 702.4 and 702.5, respectively, we derived potential ambient water quality values of 0.0067 mcg/L (oncogenic effects) and 0.011 mcg/L (nononcogenic effects) for PFOA. The most stringent of the potential values is 0.0067 mcg/L (6 NYCRR 702.4, Oncogenic Effects) and thus, this value is selected as the ambient water quality value [Health (Water Source)] for PFOA.

REFERENCES

Alaska Department of Environmental Conservation. 2018. Technical Memorandum: Action Levels for PFAS in Water and Guidance on Sampling Groundwater and Drinking Water. Last Accessed (04/04/2019) at

https://dec.alaska.gov/media/10156/pfas-drinking-water-action-levels-final.pdf.

- ATSDR (Agency for Toxic Substances and Disease Registry). 2018. Draft Toxicological Profile for Perfluoroalkyls. Last accessed (03/21/2019) at http://www.atsdr.cdc.gov/toxprofiles/index.asp#P.
- Barry V, Winquist A, Steenland K. 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 121:1313-1318.
- Bartell SM, Calafat AM, Lyu C, et al. 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect. 118(2):222–228.
- Biegel LB, Hurtt ME, Frame SR, et al. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicol Sci. 60:44-55.
- Brede E, Wilhelm M, Göen T, et al. 2010. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int J Hyg Environ Health. 213(3):217–223.
- Butenhoff JL, Gaylor DW, Moore JA, et al. 2004. Characterization of risk for general population exposure to perfluorooctanoate. Regul Toxicol Pharmacol. 39:363-380.
- Butenhoff JL, Kennedy GL Jr., Chang SC, et al. 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology. 298: 1–13.
- C8 SP (C8 Science Panel). 2017. The Science Panel Website. Last accessed (03/22/2019) at http://www.c8sciencepanel.org/index.html.
- Clewell HJ. 2006. Application of pharmacokinetic modeling to estimate PFOA exposures associated with measured blood concentration in human populations. Society for Risk Analysis Annual Meeting 2006 (Powerpoint presentation).
- Connecticut State Department of Health. 2016. Drinking Water Action Level for Perfluorinated Alkyl Substances (PFAS). Last accessed (04/04/2019) at https://portal.ct.gov/-/media/Departments-and-Agencies/DPH/dph/environmental_health/eoha/Toxicology_Risk_Assessment/DrinkingWaterActionLevel PerfluorinatedAlkylSubstances-PFAS.pdf?la=en.
- Darrow LA, Stein CR, Steenland K. 2013. Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the mid-Ohio valley, 2005-2010. Environ Health Perspect. 121:1207-1213.
- EC/HC (Environment Canada/Health Canada). 2012. Screening Assessment. Perfluorooctanoic Acid, its Salts, and its Precursors. August 2012. Last accessed (03/21/2019) at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=370AB133-1.
- EFSA CONTAM (European Food Safety Authority Panel on Contaminants in the Food Chain). 2018. Scientific Opinion: Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA Journal 16: 5194. Last accessed (04/11/2019) at https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5194.

- Gehlhaus MW, Gift JS, Hogan KA, et al. 2011. Approaches to cancer assessment in EPA's Integrated Risk Information System. Toxicol Appl Pharmacol. 254:170-180.
- Health Canada. 2018. Guidelines for Canadian Drinking Water Quality Guideline Technical Document Perfluorooctanoic Acid (PFOA). Last accessed (4/11/2019) at https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-technical-document-perfluorooctanoic-acid.html.
- HSDB (Hazardous Substances Data Bank). 2016. Perfluorooctanoic acid (PFOA). CASRN: 335-67-1. Last accessed (3/20/2019) at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
- IARC (International Agency for Research on Cancer). 2016. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Perfluorooctanoic acid. 110: 37-110. Last accessed (4/11/2019) at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono110-01.pdf.
- Lau C, Thibodeaux JR, Hanson RG, et al. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci. 90:510-518.
- Loveless SE, Finlay C, Everds NE, et al. 2006. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (AFPO). Toxicol. 220:203-217.
- Li Y, Fletcher T, Mucs D, et al. 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med. 75:46-51.
- Macon MB, Villanueva LR, Tatum-Gibbs K, et al. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: Low-dose developmental effects and internal dosimetry. Toxicol Sci. 122:134-145.
- Maine Center for Disease Control and Prevention. 2017. Summary of the 2016 Updates to the Maximum Exposure Guidelines. Last accessed (04/04/2019) at https://www.maine.gov/dhhs/mecdc/environmental-health/eohp/wells/documents/megchanges2016.pdf.
- Massachusetts Department of Environmental Protection. 2018. Massachusetts Department of Environmental Protection Office of Research and Standards Final Recommendations for Interim Toxicity and Drinking Water Guidance Values for Perfluorinated Alkyl Substances Included in the Unregulated Chemical Monitoring Rule 3. Last accessed (04/04/2019) at https://www.mass.gov/files/documents/2018/06/11/pfasors-ucmr3-recs_0.pdf.
- MDH (Minnesota Department of Health). 2018. Toxicological Summary for: Perfluorooctanoate. Health Based Guidance for Water. Health Risk Assessment Unit, Environmental Health Division. Last accessed (03/25/2019) at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf.
- Michigan Department of Environmental Quality. 2018. State Takes Action to Strengthen Environmental Criteria in Response to PFAS Contamination. January 9, 2018 Press Release. Last accessed (04/04/2019) at https://www.michigan.gov/deq/0,4561,7-135-3308-457220--,00.html.
- NJ DEP (New Jersey Department of Environmental Protection). 2007. Guidance for PFOA in Drinking Water at Pennsgrove Water Supply Company. Memorandum from Gloria Post to Barker Hamill. Last accessed (03/21/2019) at https://rucore.libraries.rutgers.edu/rutgers-lib/46540/PDF/1/play/.

NJ DEP (New Jersey Department of Environmental Protection). 2019. Technical Support Document: Interim

Specific Ground Water Criterion for Perfluorooctanoic Acid (PFOA, C8) (CAS #: 335-67-1; Chemical Structure: CF3(CF2)6COOH). Division of Science and Research. Last accessed (04/10/2019) at https://www.nj.gov/dep/dsr/supportdocs/PFOA_TSD.pdf.

- NJ DWQI (New Jersey Drinking Water Quality Institute). 2017. Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). Health Effects Subcommittee. Last accessed (03/21/2019) at https://www.nj.gov/dep/watersupply/pdf/pfoa-appendixa.pdf.
- 6 NYCRR (New York State Codes, Rules and Regulations). 2019. Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6 NYCRR, Chapter X, Parts 700 706. Last accessed (04/11/2019) at http://www.dec.ny.gov/regs/2485.html.
- Olsen GW, Burris JM, Ehresman DJ, et al. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Env Health Perspect. 115: 1298-1305.
- Quist EM, Filgo AJ, Cummings CA, et al. 2015. Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). Toxicol Path. 43:546-557.
- Raleigh KK, Alexander BH, Olsen GW, et al. 2014. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. Occup Environ Med. 71:500-506.
- Sibinski LJ. 1987. Final Report of a Two Year Oral (Diet) Toxicity and Carcinogenicity Study of Fluorochemical FC-143 (Perfluorooctanane Ammonium Carboxylate) in Rats. Vol. 1-4, 3MCompany/RIKER Exp. No.0281CR0012; 8EHQ-1087-0394, October 16, 1987. [As cited in US EPA, 2005a].
- Steenland K, Fletcher T, Savitz DA. 2010. Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). Environ Health Perspect. 118:1100-1108.
- Steenland K, Woskie S. 2012. Cohort mortality study of workers exposed to perfluorooctanoic acid. Am J Epidemiol. 176:909-917.
- Steenland K, Zhao L, Winquist A, Parks C. 2013. Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. Environ Health Perspect. 121:900-905.
- Tan YM, Clewell III HJ, Andersen ME. 2008. Time dependencies in perfluorooctylacids disposition in rats and monkeys: A kinetic analysis. Toxicol. Lett. 177:38–47.
- Tardiff RG, Carson ML, Sweeney LM, et al. 2009. Derivation of a drinking water equivalent level (DWEL) related to the maximum contaminant level goal for perfluorooctanoic acid (PFOA), a persistent water soluble compound. Food Chem Toxicol. 47:2557-2589.
- Tucker, DK, Macon, MB, Strynar, MJ, et al. 2015. The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. Reprod. Toxicol. 54: 26-36.
- US EPA (U.S. Environmental Protection Agency). 1992. Draft Report: A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of mg/kg^{3/4}day. Fed Register. 57:24152–24173.

- US EPA (U.S. Environmental Protection Agency). 2005a. Draft Risk Assessment of the Human Health Effects Associated with Exposure to Perfluorooctanoic Acid and Its Salts. Last accessed (03/21/2019) at https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/1332679.
- US EPA (U.S. Environmental Protection Agency). 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F. Last accessed (07/23/19) at https://www.epa.gov/risk/supplemental-guidance-assessing-susceptibility-early-life-exposure-carcinogens.
- US EPA (U.S. Environmental Protection Agency). 2006. SAB Review of EPA's Draft Risk Assessment of Potential Human Health Effects Associated with PFOA and Its Salts. EPA-SAB-06-006. Last accessed (03/21/2019) at https://yosemite.epa.gov/sab%5Csabproduct.nsf/A3C83648E77252828525717F004B9099/\$File/sab_06_00 6.pdf.
- US EPA (U.S. Environmental Protection Agency). 2009. Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). Last accessed (03/21/2019) at https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos.
- US EPA (U.S. Environmental Protection Agency). 2011. Exposure Factors Handbook. 2011 Edition. EPA/600/R-090/052F. Last accessed (05/23/2013) at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20563.
- US EPA (U.S. Environmental Protection Agency). 2012a. Benchmark Dose Technical Guidance. EPA/100/R-12/001. Last accessed (01/27/2014) at http://www.epa.gov/raf/publications/benchmarkdose.htm.
- US EPA (U.S. Environmental Protection Agency). 2012b. Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/011F. Last accessed (01/27/2014) at http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList&list_type=alpha&view=T.
- US EPA (U.S. Environmental Protection Agency). 2014. Health Effects Document for Perfluorooctanoic Acid (PFOA). External Review Draft. EPA Document Number: 822R14001. Last accessed (03/21/2019) at https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos.
- US EPA (U.S. Environmental Protection Agency). 2016a. Health Effects Support Document for Perfluorooctanoic Acid (PFOA). Office of Water. EPA 822-R-16-003. Last accessed (03/21/2019) at https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-health-advisories-pfoa-and-pfos.
- US EPA (U.S. Environmental Protection Agency). 2016b. Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). Office of Water. EPA 822-R-16-005. Last accessed (03/21/2019) at https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-health-advisories-pfoa-and-pfos.
- Vermont Department of Health. 2018. Memorandum: Drinking Water Health Advisory for Five PFAS (perfluorinated alkyl substances). July 10, 2018. Last accessed (04/04/2019) at http://www.healthvermont.gov/sites/default/files/documents/pdf/ENV_DW_PFAS_HealthAdvisory.pdf.

Vieira VM, Hoffman K, Shin HM, et al. 2013. Perfluorooctanoic Acid exposure and cancer outcomes in a

contaminated community: a geographic analysis. Environ Health Perspect. 121:318–323.

- Wambaugh, J.F., R.W. Setzer, A.M. Pitruzzello, J. Liu, D.M. Reif, N.C. Kleinstreuer, N. Ching, Y. Wang, N. Sipes, M. Martin, K. Das, J.C. DeWitt, M. Strynar, R. Judson, K.A. Houck, and C. Lau. 2013. Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluorooctanesulfonate. Toxicological Sciences 136:308–327
- Winquist A, Steenland K. 2014. Perfluorooctanoic acid exposure and thyroid disease in community and worker cohorts. Epidemiology. 25:255-264.
- Worley RR, Moore SM, Tierney BC, et al. 2017. Per- and polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community. Environ Int. 106:135–43.

SEARCH STRATEGY

We reviewed publications by various state, federal, or international public health agencies (listed in fact sheet references) and identified important papers from the list of references within each document. Before and on April 10, 2019, we also searched the biomedical literature using PubMed (U.S. National Library of Medicine) and the search term "PFOA and toxicity".

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EXHIBITS

- Exhibit 1. US EPA (2016) Reference Dose Derivation and Lifetime Drinking Water Health Advisory for Perfluorooctanoic Acid.
- Exhibit 2. MDH (2018) Derivation of Reference Dose and Health-Based Water Value Concentration for Perfluorooctanoic Acid.
- Exhibit 3. NJ DWQI (2017) Health-based MCL for Perfluorooctanoic Acid
- Exhibit 4. List of Abbreviations and Acronyms Frequently Used in New York State Human Health Fact Sheets.

PFOA Administered Dose (mg/kg/day)	0	1.3	14.2
Testicular Tumor (Leydig cell adenoma) Incidence	0/49	2/50	7/50 ^b

Table 1. Exposure Response Data for Testicular Tumors in Male Sprague Dawley Rats.^a

^aTumor incidence data come from Table 8 of the Butenhoff et al. (2012) study and from Table 5 of Tardiff et al. (2009). ^bStatistically significant ($p \le 0.05$) compared to controls.

	Risk-Specific	Cancer Potency	Extrapolati	on Methods	
Agency	Dose ^a (mg/kg-day)	Factor (mg/kg-day) ⁻¹	High to Low Dose	Animal to Human	Summary
NYS (derived under 6 NYCRR 702.4)	1.9 x 10 ⁻⁷	5.3	linearized multistage model with linear extrapolation from the point of departure	single- compartment human PBPK model	Based on Leydig cell tumors in male rats exposed to APFO via the diet for two-years. Tardiff et al. (2009) used PBPK model to estimate area under the curve PFOA serum concentrations in male rats from administered doses.
US EPA (2016a)	1.4 x 10 ⁻⁵	0.07	multistage model with linear extrapolation from the point of departure	$\mathrm{BW}^{3/4\mathrm{b}}$	Based on Leydig cell tumors in male rats exposed to APFO via the diet for two-years. The CPF was derived from a BMDL ₀₄ of 1.99 mg/kg-day.
NJ DWQI (2017)	4 x 10 ⁻⁷	2.5	dose-response models with linear extrapolation from the point of departure	chemical specific PK adjustment factor of 120	Based on Leydig cell tumors in male rats exposed to APFO via the diet for two-years. The CPF is based on the average of two BMDL ₀₅ values (2.36 mg/kg-day) and a chemical specific pharmacokinetic (PK) factor of 120 based on the ratio between the estimated serum half-lives in humans and male rats [i.e., human serum $\frac{1}{2}$ life (840 days) \div serum $\frac{1}{2}$ life in rats (7 days) = 120].
Health Canada (2018)			uncertainty factors	chemical- specific UF of 17 (pharmaco- kinetics) ^c	Based on Leydig cell tumors in male rats exposed to APFO via the diet for two-years. Using a noncancer threshold approach, Health Canada calculated a TDI of 0.003 mg/kg-day for carcinogenicity based on weight of evidence that "suggests that PFOA is a non-mutagenic compound." The TDI is based on a NOEL of 1.3 mg/kg-day and a total UF of 25 (2.5 for interspecies pharmacodynamics and an intraspecies UE of 10

 Table 2. Authoritative Body Cancer Potency Estimates for PFOA.

^aThe dose associated with an excess lifetime cancer risk of one-in-one million (i.e., $1 \ge 10^{-6}$ dose), where, $1 \ge 10^{-6}$ dose = $1 \ge 10^{-6}$ /cancer potency factor.

^b Factor for dose adjustment from animals to humans is (male rat body weight/human body weight)^{1/4}. ^cHealth Canada (2018) calculated a chemical specific pharmacokinetic adjustment factor of 17 based on differences in PBPK modeled steady-state plasma PFOA predictions at 1 mg/kg-day between humans and rats [i.e., chemical specific UF = human steady state PFOA plasma level (1493 micrograms per milliliter (mcg/mL)) ÷ estimated rat steady state PFOA plasma level (89.5 mcg/mL) = 17].

	Reference	Point of Depa	rture		
Agency ^a	Dose ^b (mg/kg-day)	Dose or Blood Concentration	Basis	UF	Summary
US EPA° (2016)	2.0 x 10 ⁻⁵	38 mg/L in blood serum (mice); HED _{LOEL} = 0.0053 mg/kg-day	serum LOEL	300	Based on reduced ossification and accelerated male puberty in mice exposed on gestational days 1 to 17. Total UF of 300 to account for interspecies differences in pharmacodynamics (3), use of a LOEL (10) and intraspecies (human) variability (10). See Exhibit 1.
MDH (2018)	2.0 x 10 ⁻⁵	38 mg/L in blood serum (mice); HED _{LOEL} = 0.0053 mg/kg-day	serum LOEL	300	Based on reduced ossification and accelerated male puberty in mice exposed on gestational days 1 to 17. Total UF of 300 to account for interspecies differences in pharmacodynamics (3), use of a LOEL (3), intraspecies (human) variability (10), and database inadequacies (3). See Exhibit 2.
NJ DWQI (2017)	2.0 x 10 ⁻⁶	4.35 mg/L in blood serum (mice), approximately equivalent to 0.00061 mg/kg-day	serum BMSL ₁₀	300	Based on increased relative liver weights in mice exposed for 14 days. Total UF of 300 to account for interspecies differences in pharmacodynamics (3), intraspecies (human) variability (10), and database inadequacies (10). See Exhibit 3.

Table 3. Reference Doses for PFOA Derived by Authoritative Bodies.

^aThe European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM) derived a tolerable weekly intake of 6 ng/kg-week for PFOA (equivalent to 0.9 ng/kg-day) based on increased total serum cholesterol in human epidemiological studies as part of a scientific opinion on the risks of PFOA in food. There is no clear consensus among health agencies on whether cross-sectional studies such as those used by EFSA CONTAM in a weight of evidence approach provide sufficient evidence to establish causality, and whether the study limitations preclude their use for quantitative risk assessment (NJ DWQI, 2017; ATSDR 2018). Limitations in the approach used by EFSA included use of data packaged in quantiles rather than raw data points for benchmark dose modeling, and no adjustments for co-exposures to other perfluoroalkyl compounds. Based on these considerations, the EFSA derivation was not considered further as a basis for a potential ambient water quality value.

^bAgencies use different terms for the reference dose, including acceptable daily intake or dose, tolerable daily intake, and minimal risk level.

^cSeveral agencies, including the Alaska Department of Environmental Conservation (2018), Connecticut State Department of Public Health (2016), Maine Center for Disease Control and Prevention (2017), Massachusetts Department of Environmental Protection (2018), Michigan Department of Environmental Quality (2018), and the Vermont Department of Health use the US EPA reference dose and/or lifetime health advisory to define a health-based guidance value for PFOA in drinking water.

US EPA (2016) REFERENCE DOSE DERIVATION AND LIFETIME DRINKING WATER HEALTH ADVISORY FOR PERFLUOROOCTANOIC ACID.

Source: US EPA (U.S. Environmental Protection Agency). 2016. Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). Office of Water. EPA 822-R-16-005. Last accessed (03/21/2019) at https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-health-advisories-pfoa-and-pfos.

5.0 DOSE-RESPONSE ASSESSMENT

As an initial step in the dose-response assessment, EPA identified a suite of animal studies with NOAELs and/or LOAELs that identified them as potential candidates for development of the RfD for PFOA. These studies included short-term, subchronic, and chronic exposures, including developmental and reproductive toxicity studies. The available studies evaluated endpoints including liver effects (weight changes with histopathology), body weight changes in adults and offspring, reproductive outcomes such as fertility, developmental effects (altered puberty, survival, and developmental delays such as eve opening), and immune effects. The candidate studies were selected based on their NOAEL and/or LOAEL values, a duration of 11 to 91 days, use of a control, and two or more doses. From these studies, those that presented serum data amenable for modeling (i.e., determination of HEDs) were selected for dose-response analysis. The subset of studies amenable for use in deriving HED based on average serum measurements from the pharmacokinetic model is limited because of the need to have dose and species-specific serum values for model input as well as exposure durations of sufficient length to achieve values near to steady-state projections or applicable to developmental endpoints with lifetime consequences following short-term exposures. The pharmacokinetically modeled average serum values from the animal studies are restricted to the animal species selected for their low dose response to oral PFOA intakes.

As described in section 3.2.4, EPA used the Wambaugh et al. (2013) pharmacokinetic model to derive the average serum concentrations associated with the candidate NOAELs and LOAELs from the toxicological database. Studies with serum information for each of the doses that demonstrated dose response and were amendable for modeling of the area under the curve (AUC) at the time of sacrifice were used. The AUC results were converted to average serum values at the time of sacrifice with consideration of the duration of exposure. The average serum values were converted to the HED, as described further below.

The data were analyzed within a Bayesian framework using a Markov Chain Monte Carlo sampler implemented as an R statistical analysis package developed by EPA to allow predictions across species, strains, and genders, and to identify serum levels associated with the external doses at the NOAEL and LOAEL. The model predictions were evaluated by comparing each predicted final serum concentration to the serum value measured in the supporting animal studies.

The average serum concentrations were converted into an oral equivalent dose by recognizing that clearance from the body equals dose to the body. Clearance can be calculated if the rate of elimination (derived from half-life) and the volume of distribution are both known. EPA used the Bartell et al. (2010) calculated human half-life of 2.3 years (general population) with the Thompson et al. (2010) volume of distribution (V_d) of 0.17 L/kg body weight (bw) to determine a clearance of 1.4×10^{-4} L/kg bw/day by the following equation:

 $CL = V_d x (ln 2 \div t_{\frac{1}{2}}) = 0.17 L/kg bw x (0.693 \div 839.5 days) = 0.00014 L/kg bw/day$

Where:

V_d = 0.17 L/kg In 2 = 0.693 t% = 839.5 days (2.3 years x 365 days/year = 839.5 days)

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Multiplying the derived average serum concentrations (in µg/mL) for the NOAELs and LOAELs identified in the key animal studies by the clearance value predicts oral HEDs in mg/kg bw/day for each corresponding serum measurement. The HED values are the predicted human oral exposures necessary to achieve serum concentrations equivalent to the NOAEL or LOAEL in the animal toxicity studies using linear human kinetic information.

Table 5-1 provides the NOAEL, LOAEL, and effect information from those studies, along with the associated average serum values and the percent of steady state represented by the LOAEL.

Study	Dosing duration days	NOAEL mg/kg/d	NOAEL Av serum mg/L	HED mg/kg/d	LOAEL mg/kg/d	LOAEL (Av serum) mg/L	HED mg/kg/d
DeWitt et al. (2008): mice; 1 IgM response to SRBC	15	1.88	38.2	0.0053	3.75	61.9	0.0087
Lau et al. (2006): mice decreased ↓ pup ossification (m, f), accelerated male puberty	17	None	1		1	38.0	0.0053
Palazzolo et al. (1993); Perkins et al. (2004): rats; †liver weight/necrosis	91	0.64	31.6	0.0044	1.94	77.4	0.0108
Wolf et al. (2007): mice; GD 1–17 JPup body weight	17	None	35	8	3	77.9	0.0109
Wolf et al. (2007): mice; GD 7-17 µPup body weight ¹	n	None	12.1		5	87.9	0.0123
Butenhoff et al. (2004a): 1 relative body weight/† relative kidney weight and †kidney: brain weight ratio in F0 and F1 at sacrifice	84	None		-	1	45.9	0.0064

Table 5-1. Human Equivalent Doses Derived from the Modeled Animal Average Serum Values

Significance p < 0.05 or p < 0.01

m = male; f = female; SRBC = sheep red blood cell; IgM = immunoglobulin M; GD = gestation day

1 serum from pups on PND 22

The external doses in each of the studies varied. The NOAELs ranged from 0.64 to 1.88 mg/kg/day. The corresponding average serum values ranged from 1.6 mg/L (rat) to 38.2 mg/L (mouse). At the LOAEL, the average serum values range from 38 μ g/mL (mouse) to 87.6 μ g/mL (monkey) at doses estimated to represent about 56% to 96% of steady state. At the low end of the range the effects of concern are observed in neonates (low birth weight, delays in developmental endpoints, with increased kidney weight at sacrifice later in life).

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Much of the variability in the average serum levels for the LOAELs was due to differences in the doses used in the individual studies. For example, two of the modeled endpoints (Wolf et al. 2007) identified low birth weights in mouse pups as the critical effect, but had a single external dose that was 3 to 5 times higher than the low dose from the Lau et al. (2006) mouse study (1 mg/kg/day).

Among the studies conducted in mice, dose was a more important variable in determining serum level and percent of steady state than duration of exposure. This is a characteristic of the nonlinear toxicokinetics exhibited by PFOA. The half-life for doses that exceed the resorption capacity of the kidney are shorter than lower doses that can be resorbed and thereby persist in serum over a longer exposure duration. For example, in Wolf et al. (2007), an 11-day dose of 5 mg/kg/day resulted in an average serum of 88 mg/L (82% of concentration at steady state or Css) whereas a 1 mg/kg/day dose for 17 days resulted in an average serum of 38 mg/L (56% of Css). In rats, dosed at 1 mg/kg/day, over two generations (84 days), an average serum of 45.9 mg/L at 87% of steady state was determined (Butenhoff et al. 2004a). A 91-day exposure (Palazzolo et al. 1993/Perkins et al. 2004) to 1.94 mg/kg/day resulted in a serum value of 77 mg/kg/day and was 91% of steady state. The endpoints in Butenhoff et al. (2004a) are effects on body weight and relative kidney weight in the adult F0 and F1 rats, while the endpoint for Palazzolo et al. (1993)/Perkins et al. (2004) was systemic increased liver weight with lower-level necrosis.

Assuming that MOA and susceptibility to toxicity do not vary and that pharmacokinetics alone explains variation, it is reasonable to expect similar concentrations to cause similar effects in humans and are more important than both dose and duration once steady state is attained.

5.1 Uncertainty Factors

An uncertainty factor for intraspecies variability (UF_B) of 10 is assigned to account for variability in the responses within the human populations because of both intrinsic (toxicokinetic genetic, life stage, health status) and extrinsic (life style) factors that can influence the response to dose. No information was available relative to variability in the human population that supports a factor other than 10.

An uncertainty factor for interspecies variability (UF_A) of 3 is applied to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). The 3-fold factor is applied to account for toxicodynamic differences between the animals and humans. The HEDs were derived using average serum values from a model to account for toxicokinetic differences between animals and humans.

An uncertainty factor for LOAEL to NOAEL extrapolation (UFL) of 10 is applied to all PODs other than the Palazzolo et al. (1993)/Perkins et al. (2004) and DeWitt et al. (2008) studies to account for use of a LOAEL for the POD. The POD for the Palazzolo et al. (1993)/Perkins et al. (2004) and DeWitt et al. (2008) studies are NOAELs for the effect identified as critical.

An uncertainty factor for extrapolation from a subchronic to a chronic exposure duration (UFs) of 1 is applied because the PODs are based on average serum concentrations and determined to represent >80% of steady state for each study (81–91%), except for the Lau et al. (2006) developmental study (56%). The Lau et al. (2006) developmental HED was not adjusted

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for lifetime exposures because the average serum values associated with the developmental studies are more protective than those for the longer-term studies of systemic toxicity. A UFs of 10 was applied to the DeWitt et al. (2008) study serum derived HED reflecting (74%) of steady state because the data suggest that longer term exposures to the same dose have the potential to increase serum values beyond the levels indicated by the 15-day study. In addition, the NOAEL for immunological effects (0.94 mg/kg/day) was a LOAEL for effects on liver weight in the absence of histological evaluation on both days 16 and 31 following a 15-day exposure (DeWitt et al. 2008). Thus, there is a potential that lifetime exposures at steady state can affect the liver and increase the risk for tissue damage.

A database uncertainty factor (UF_D) of 1 was applied to account for deficiencies in the database for PFOA. There are extensive human data from epidemiological data from the general population as well as worker cohorts. The epidemiology data provide strong support for the identification of hazards observed following exposure to PFOA in the laboratory animal studies and human relevance. However, uncertainties in the use of the available epidemiology data precluded their use at this time in the quantification of the effect level for derivation of the drinking water HA. In animals, acute, short term, subchronic and chronic studies, including a long term cancer study, are available. In addition, several developmental studies and a two-generation reproductive toxicity study evaluating exposure of pregnant dams and offspring to PFOA are available.

5.2 RfD Determination

Table 5-2 provides the calculations for candidate RfDs using the HEDs derived from the NOAEL or LOAEL average serum concentrations using pharmacokinetic modeling based on the serum values measures collected at animal sacrifice. Uncertainty factors (see section 5.1) were applied to each POD, and Table 5-2 illustrates the array of candidate RfD outcomes. Each POD is affected by the doses used in the subject study, the endpoints monitored, and the animal species/gender studied. Thus, the array of outcomes, combined with knowledge of the individual study characteristics helps to inform selection of an RfD that will be protective for humans. Other than DeWitt et al. (2008) and Lau et al. (2006), all of the selected studies had serum levels that had reached > 80% of Css. It is important to note the relatively narrow range of RfDs across the multiple endpoints and study durations evaluated.

Using the pharmacokinetic model of Wambaugh et al. (2013), average serum PFOA concentrations were derived from AUC considering the number of days of exposure before sacrifice. The predicted serum concentrations were converted as described above to oral HEDs mg/kg/day for each corresponding serum measurement. The candidate RfDs in Table 5-2 range from 0.00002 to 0.00015 mg/kg/day across multiple endpoints. The RfD of 0.00002 mg/kg/day calculated from HED average serum values from Lau et al. (2006) was selected. This RfD is derived from reduced ossification of the proximal phalanges (forelimb and hindlimb) and accelerated puberty in male pups (4 days earlier than controls) as the critical effects. The POD for the derivation of the RfD for PFOA is the HED of 0.0053 mg/kg/day that corresponds to a LOAEL that represents approximately 60% of steady-state concentration. An UF of 300 (10 UFH, 3 UFA, and 10 UFL) was applied to the HED LOAEL to derive an RfD of 0.00002 mg/kg/day.

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POD	HED POD mg/kg/day	UFB	UFA	UFL	UFs	UFD	UFtatal	Candidate RfD mg/kg/day
PK-HED _{NOAEL} Palazzolo et al. (1993)/Perkins et al. (2004) rats; †liver weight/necrosis	0.0044	10	3	245			30	0,00015
PK-HEDLOAEL Wolf et al. (2007) GD1-17 mice; Pup body weight	0.0109	10	3	10		10	300	0.00004
PK-HED _{LOAFL} Wolf et al. (2007) GD 7-17 mice; 1Pup body weight (serum from pups on PND 22)	0.0123	10	3	10	-	198	300	0.00004
PK-HED _{NOAEL} DeWitt et al. (2008) mice; ↓ IgM response to SRBC	0.0053	10	3	85	10	33	300	0.00002
PK-HED _{LOAFL} Lau et al. (2006) mice decreased ↓ pup ossification (m, f), accelerated male puberty	0.0053	10	3	10	-		300	0.00002
PK-HEDLOAEL Butenhoff et al. (2004a) ↓ relative body weight/↑ relative kidney weight and †kidney: brain weight ratio in F0 and F1 at sacrifice	0.0064	10	3	10			300	0.00002

Table 5-2. Candidate RfDs Derived from the HEDs from the Pharmacokinetic Model Average Serum Values

Notes.

PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestation day; IgM = immunoglobulin M; m = male; f = female; SRBC = sheep red blood cell; UFn = intraindividual uncertainty factor; UFA = interspecies uncertainty factor; UFs = subchronic to chronic uncertainty factor; UFL = LOAEL to NOAEL uncertainty factor; UFn = incomplete database uncertainty factor; UFs = total (multiplied) uncertainty factor

Decreased pup body weights also were observed in studies conducted by Wolf et al. (2007), White et al. (2009), and Lu et al. (2015) using mice receiving external doses within the same order of magnitude (1, 3, and 5 mg/kg/day respectively) as those chosen for the RfD. The selected RfD from the reproductive and developmental studies is supported by the longer term RfD for effects on the response of the immune system to external challenges as observed following the short-term exposures to mature mice and the effects on kidney weight observed at the time of sacrifice in the F0 and F1 adult males that provided the serum in the Butenhoff et al. (2004a) study (DeWitt et al. 2008).

Support for the selected RfD also is provided by other key studies with NOAELs and LOAELs similar to those used for quantification, but lacking serum data that could be used for modeling. There were effects on liver weight and hepatic hypertrophy in the Perkins et al. (2004) and DeWitt et al. (2008) studies that were modeled but not considered in the derivation of the

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RfD because of a lack of data to demonstrate adversity as determined by the Hall et al. (2012) criteria at the dose causing the liver effects but not the effects identified as critical. The LOAEL for evidence of hepatic necrosis and other signs of tissue damage in the F1 male rat pups from the Butenhoff et al. (2004a) study was 3 mg/kg/day; the NOAEL was 1 mg/kg/day. In the Loveless et al. (2008) study, the LOAEL for increased relative liver weight accompanied by focal liver necrosis in male rats was 10 mg/kg/day and the NOAEL was 1 mg/kg/day, while in male mice, the LOAEL for the same effect was 1 mg/kg/day and the NOAEL was 0.3 mg/kg/day following a 29-day exposure. In the study by Tan et al. (2013), the degree of damage to the liver at 5 mg/kg/day became more severe with increased necrosis, inflammation, and steatosis when animals were given a high-fat diet. The HED modeled from the average serum value in mice for the LOAEL (3 mg/L) from Wolf et al. (2007) and White et al. (2009) was 0.0110 mg/kg/day, about twice that for the rats in the Lau et al. (2006) study (0.0053 mg/kg/day). Both studies lacked a NOAEL. Each of these data sets support LOAELs for the critical study by Lau et al. (2006) selected for RfD derivation and, as a consequence, the HED derived from modeled average serum values.

6.0 HEALTH ADVISORY VALUES

6.1 Relative Source Contribution

As described in section 2.2 and below, humans can be exposed to PFOA and precursor chemicals via multiple sources, including air, food, and consumer and industrial products (including textiles and rugs). The most common route of exposure to PFOA is via the diet, followed by indoor dust, especially for children.

Food is a significant source of exposure to PFOA: It has been detected in a variety of foods including snack foods, vegetables, meat, dairy products, human breast milk, and fish. Occurrence in food products can result from the use of contaminated water in processing and preparation; growth of food in contaminated soils; direct and indirect exposures of domestic animals to PFOA from drinking water, consumption of plants grown in contaminated soil, and through particulate matter in air; fish from contaminated water ways; and packaging materials.

PFOA has been detected in finished drinking water samples collected by EPA and others. PFOA is not regulated under the SDWA and was included in EPA's UCMR 3. PFOA was detected at a small number of PWSs (0.9%) through this monitoring program. Therefore, there is potential exposure to PFOA from drinking water ingestion.

The vapor pressure of PFOA indicates that volatilization is low; however, PFOA can be released into the atmosphere from industrial and municipal waste incinerators and adsorb to airborne particulates. It can be transported long distances through the atmosphere and has been detected globally at low concentrations. Inhalation of PFOA is possible, and it has been measured in indoor air in residential, commercial, and office settings because of its use in carpets, textiles, paint, furniture, and other consumer products. Both air and dust can be a vehicle for volatile telomer alcohols that metabolically degrade to PFOA. Given the widespread commercial and industrial use of PFOA and its physical properties, air is a potential source of exposure to it and the C8:2 telomer alcohol precursors.

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PFOA also has been detected in soils and dust from carpets and upholstered furniture in homes, offices, and vehicles. Incidental exposure from soils and dust is an important exposure route, particularly for small children because of their hand-to-mouth behaviors. Also, the levels in soils and surface waters can affect the concentrations in local produce, meat/poultry, dairy products, fish, and particulates in the air.

In summary, based on the physical properties and available exposure information for PFOA, there are many are potential sources. Following EPA's Exposure Decision Tree in its 2000 methodology (USEPA 2000), significant potential sources other than drinking water ingestion exist; however, information is not available to quantitatively characterize exposure from all of these different sources (Box 8B in the Decision Tree). Therefore, EPA recommends an RSC of 20% (0.20) for PFOA.

6.2 Lifetime Health Advisory

Based on the consistency of the responses across the chronic studies and those for reproductive and developmental endpoints, and with recognition of the use of developmental toxicity as the most sensitive endpoint, 0.00002 mg/kg/day was selected as the RfD for PFOA. This value is based on the HED for developmental effects (reduced ossification in male and female pups and accelerated puberty in male pups) from the Lau et al. (2006) study. The RfD that serves as the POD for the lifetime HA is applicable for effects other than those occurring during development. The candidate RfD values derived from the two-generation study by Butenhoff et al. (2004a) for effects on adult body weight plus relative liver and kidney weights in F0 and F1 male rats is the same as the value based on the developmental effects observed by Lau et al (2006). The candidate RfD from the DeWitt et al. (2008) study for suppression of the immunological response to a challenge is the same as that from Lau et al. (2006).

Due to the potential increased susceptibility during the time period of pregnancy and lactation, EPA used drinking water intake and body weight parameters for lactating women in the calculation of a lifetime HA for this target population during this potential critical time period. EPA used the rate of 54 mL/kg-day representing the consumers only estimate of combined direct and indirect community water ingestion at the 90th percentile for lactating women (see Table 3-81 in USEPA 2011b). Comparing the pregnant woman and the lactating woman, the lactating woman is the more protective scenario given her increased water intake rate for her body weight needed to support milk production. Additionally, human studies demonstrate that PFOA is transferred from mother to infant via cord blood and breast milk. A recent study showed that breast milk contributed > 83% of the PFOA exposure in 6-month-old infants (Haug et al. 2011).

The exposure factors applied to the RfD to derive the lifetime HA are specific to the most sensitive population and will be protective of pregnant women as well as of the general population. Thus, the protection conferred by the lifetime HA is broadly protective of public health.

The lifetime HA for PFOA is calculated as follows:

A DWEL is derived from the RfD and assumes that 100% of the exposure comes from drinking water.

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$DWEL = \frac{RfD \ x \ bw}{DWI}$

 $DWEL = \frac{0.00002 \text{ mg/kg/day}}{0.054 \text{ L/kg-day}} = 0.00037 \text{ mg/L}$

Where:

RfD = 0.00002 mg/kg/day; based on the LOAEL for reduced ossification of the proximal phalanges (forelimb and hindlimb) in male and female pups and accelerated (4 days earlier than controls) puberty in male pups of dams exposed to PFOA by gavage on gestation days 1 to 17 and sacrificed at weaning (Lau et al. 2006).

DWI/bw = 0.054 L/kg-day; 90th percentile consumers only estimate of combined direct and indirect community water ingestion for lactating women (see Table 3-81 in USEPA 2011b).

The lifetime HA is calculated after application of a 20% RSC (see section 6.1) as follows:

Lifetime HA = DWEL x RSC

= 0.00037 mg/L x 0.2= 0.000074 mg/L (rounded to 0.00007 mg/L) = $0.07 \mu \text{g/L}$

The lifetime HA for PFOA is based on effects (reduced ossification in male and female pups and accelerated puberty in male pups) on the developing fetus resulting from exposures that occur during gestation and lactation. These developmental endpoints are the most protective for the population at large and are effects that can carry lifetime consequences for a less than lifetime exposure. Developmental toxicity endpoints (following less than chronic exposures during a defined period of gestation or lactation) can be analyzed in both acute and chronic exposure scenarios. Because the developing organism is changing rapidly and is vulnerable at various stages in development, a single exposure at a critical time in development can produce an adverse effect (USEPA 1991). Additionally, PFOA is extremely persistent in both the human body and the environment; thus, even a short-term exposure results in a body burden that persists for years and can increase with additional exposures.

Because the critical effect identified for PFOA is a developmental endpoint and can potentially result from a short-term exposure during a critical period of development, EPA concludes that the lifetime HA for PFOA is applicable to both short-term and chronic risk assessment scenarios. Thus, the lifetime HA of 0.07 µg/L also applies to short-term exposure scenarios (weeks to months) to PFOA in drinking water, including during pregnancy and lactation.

Adverse effects observed following exposures to PFOA and PFOS are the same or similar and include effects on serum lipids, birth weight, and serum antibodies in humans. Among the animal studies, there are common effects on the liver, neonate development, and responses to immunological challenges. Both compounds also were associated with tumors in long-term animal studies. The effects that serve as the basis for the RfDs for both PFOA and PFOS are developmental endpoints (reduced ossification and accelerated puberty in males for PFOA and decreased pup birth weight for PFOS (USEPA 2016a, 2016b). Because the RfDs for both PFOA

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and PFOS are based on similar developmental effects and are numerically identical, where these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the HA (0.07 µg/L).

MDH (2018) DERIVATION OF REFERENCE DOSE AND HEALTH-BASED WATER VALUE FOR PERFLUOROOCTANOIC ACID

Source: MDH (Minnesota Department of Health). 2018. Health Based Guidance for Water. Health Risk Assessment Unit, Environmental Health Division. Last accessed (03/25/2019) at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf



Health Based Guidance for Water Health Risk Assessment Unit, Environmental Health Division 651-201-4899

Adopted as Rule: August 2018

Toxicological Summary for: Perfluorooctanoate

CAS: 45285-51-6 (anion) 335-67-1(free acid) 335-66-0 (acid fluoride) 3825-26-1 (ammonium salt, APFO) 2395-00-8 (potassium salt) 335-93-3 (silver salt) 335-95-5 (sodium salt)

Synonyms: PFOA, Perfluorooctanoic acid

MDH conducted a focused re-evaluation that used the EPA's Health Effects Support Document for Perfluorooctanoic Acid (PFOA) released in May 2016 (US EPA 2016a) as a starting point. MDH identified additional studies and conducted supplemental analysis to comply with MDH's methodology.

Short-term, Subchronic and Chronic* - Non-Cancer Health Risk Limit (nHRL) = 0.035 µg/L**

*Due to the highly bioaccumulative nature of PFOA and human half-life of approximately 2- 3 years, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV was not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. Therefore a single HBV has been recommended for short-term, subchronic, and chronic durations. The 2017 HBV was derived using a toxicokinetic (TK) model developed by MDH with input from an external peer review panel. See details about the model presented below.

**Relative Source Contribution (RSC): based on current biomonitoring serum concentrations from local and national general populations to represent non-water exposures, an RSC of 0.5 (50%) was selected for water ingestion.

Intake Rate: In keeping with MDH's practice, 95th percentile water intake rates (Table 3-1 and 3-3, US EPA 2011) or upper percentile breastmilk intake rates (Table 15-1, US EPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFOA breastmilk transfer factor of 5.2%. The intake rates and breastfeeding period of one year were used as representative of a reasonable maximum exposure scenario.

MDH typically uses a simple equation to calculate HBVs at the part per billion level with results rounded to one significant digit. However, the toxicokinetic model used to derive the HBV for PFOA

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showed that serum concentrations were impacted by changes in water concentrations at the part per trillion level. As a result, the HBV contains two digits.

Reference Dose/Concentration:	HED/Total UF = $0.0053/300=0.000018 \text{ mg/kg-d}$ (CD-1 Mice). [The corresponding serum concentration is $38/300 = 0.13 \text{ mg/L}$ (or $\mu \text{g/mL}$). NOTE: this serum concentration is inappropriate to use for individual assessment.***]
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	38 mg/L serum concentration (US EPA 2016a predicted average serum concentration for maternal animals from Lau et al 2006)
Dose Adjustment Factor (DAF):	0.00014; Toxicokinetic Adjustment based on Chemical- Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.17 L/kg x (0.693/840 days) = 0.00014 L/kg-day (US EPA 2016a)
Human Equivalent Dose (HED):	POD x DAF = 38 mg/L x 0.00014 L/kg/day = 0.0053 mg/kg- day
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability. With the exception of accelerated preputial separation (PPS), the effects observed at the LOAEL were mild. A LOAEL-to-NOAEL uncertainty factor of 3 was used, along with a database uncertainty factor of 3 for the lack of an acceptable 2-generation study.
Critical effect(s):	Delayed ossification, accelerated PPS in male offspring, trend for decreased pup body weight, and increased maternal liver weight
Co-critical effect(s):	In offspring exposed during development: changes in liver weight, histology, and triglycerides, and delayed mammary gland development.
	In adult animals: liver weight changes accompanied by changes in liver enzyme levels, changes in triglyceride and cholesterol levels, and microscopic evidence of cellular damage, decreased spleen weight, decreased spleen lymphocytes, and decreased IgM response, and kidney weight changes.
Additivity endpoint(s):	Developmental, Hepatic (Liver) system, Immune system, and Renal (Kidney) system.

*** Serum concentration is useful for informing public health policy and interpreting population-based exposures. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

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Toxicokinetic Model Description:

Serum concentrations can be calculated from the dose and clearance rate using the following equation. This equation was used by EPA, to calculate the HEDs from the POD serum concentrations.

Serum Concentration
$$\left(\frac{mg}{L}\right) = \frac{Dose\left(\frac{mg}{kg \cdot day}\right)}{Clearance Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Level in Water or Breastmilk (mg/L) and

Clearance (L/kg-d) = Volume of distribution (L/kg) x (Ln 2/half-life (days))Two exposure scenarios were examined: 1) an infant fed with formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer (maternal serum concentration x 87%) based on average cord to maternal serum concentration ratios reported in the literature. The serum concentration of the mother at delivery was assumed to be at steady-state.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A breastmilk transfer factor of 5.2%, based on average breastmilk to maternal serum concentration ratios reported in the literature, was used to calculate breastmilk concentration. According to the 2016 Breastfeeding Report Card (CDC 2016) nearly 66 percent of mothers in Minnesota report breastfeeding at six months, with 31.4 percent exclusively breastfeeding. The percent breastfeeding dropped to 41% at twelve months. MDH selected an exclusive breastfeeding duration of one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

$$Serum \ Conc.\left(\frac{mg}{L}\right) = \left[Prev. \ day \ Serum \ Conc.\left(\frac{mg}{L}\right) + \frac{Today's \ Intake(mg)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

To maintain mass balance, daily maternal serum concentrations and loss-of-chemical via transfer to the infant as well as excretion represented by the clearance rate, were calculated.

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Summary of Model Parameters

Model Parameter	Value Used
Half-life	840 days (US EPA 2016a)
Volume of distribution (Vd)	0.17 L/kg (US EPA 2016a)
Vd Age Adjustment Factor	2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961)
Clearance Rate (CR)	0.00014 L/kg-d, calculated from Vd x (Ln 2/half-life)
Placental transfer factor (% of maternal serum level)	87% (MDH 2017b)
Breastmilk transfer factor (% of maternal serum level)	5.2% (MDH 2017b)
Water Intake Rate (L/kg-d)	95 th percentile consumers only (default values, MDH 2008) (Table 3-1 & 3-3, US EPA 2011)
Breastmilk Intake Rate (L-kg-d)	Upper percentile exclusively breast-fed infants (Table 15-1, US EPA 2011)
Body weight (kg)	Calculated from water intake and breastmilk intake rate tables

A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in US EPA 2000 to derive appropriate RSCs. MDH relied upon the percentage method to reflect relative portions of water and non-water routes of exposure. The values of the duration-specific default RSCs (0.5, 0.2, and 0.2 for short-term, subchronic, and chronic, respectively) are based on the magnitude of contribution of these other exposures that occur during the relevant exposure duration (MDH 2008). However, in the case of PFOA, application of an RSC needs to account for the long elimination half-life, such that a person's serum concentration at any given age is not only the result of his or her current or recent exposures within the duration of concern, but also from exposure from years past.

Serum concentrations are the best measure of cumulative exposure and can be used in place of the RfD in the Decision Tree process. Biomonitoring results for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2017) can be used to represent non-water exposures. MDH selected an RSC of 50% for exposure from water ingestion based on:

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- A high-end, conservative estimate of background, non-water exposures represented by the 95th percentile serum concentration from 2013-14 NHANES (0.00557 mg/L serum), and
- The USEPA Decision Tree RSC ceiling of 80% to ensure a margin of safety to account for possible unknown sources of exposure

As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water through life.

For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water below an RSC of 50% throughout life is 0.15 μ g/L. Because of the long half-life, the serum concentration curve is very flat and even a small increment increase in the water concentration (0.16 μ g/L) raises the serum concentration above the 50 percent threshold for over a year.



Applying this water concentration of 0.15 μ g/L in the context of a breast-fed infant resulted in not only an exceedance of the 50% RSC threshold, but of the entire reference serum concentration for more than four years. In order to maintain a serum concentration at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.035 μ g/L.

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Due to chronic bioaccumulation in the mother and subsequent transfer to breastmilk, the breast-fed infant exposure scenario is the most limiting scenario in terms of water concentrations. To ensure protection of all segments of the population, the final health-based value for PFOA is set at 0.035 µg/L.

NJ DWQI (2017) HEALTH-BASED MCL FOR PERFLUOROOCTANOIC ACID

Source: NJ DWQI (New Jersey Drinking Water Quality Institute). 2017. Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). Health Effects Subcommittee. Last accessed (03/21/2019) at https://www.nj.gov/dep/watersupply/pdf/pfoa-appendixa.pdf.

Potential Health-based MCL based on increased relative liver weight

Increased relative liver weight is a well-established toxicological effect of PFOA in both non-human primates and rodents and is more sensitive than most other toxicological effects. Increased liver weight occurs in newborn animals after *in utero* exposure, during early life from lactational exposure, and from exposures during adulthood. As discussed in the <u>Mode of Action</u> section, PFOA may cause increased relative liver weight through multiple biochemical and cellular pathways. Increased relative liver weight can co-occur with and/or progress to other types of hepatic toxicity and is considered relevant to humans for the purposes of risk assessment.

According to USEPA IRIS guidance (USEPA, 2012c), endpoints that are "adverse, considered to be adverse, or a precursor to an adverse effect" are appropriate as the basis for non-cancer risk assessment. The increased relative liver weight caused by PFOA is usually accompanied by hepatocellular hypertrophy, and it can co-occur with and/or progress to more severe hepatic effects including hepatocellular necrosis, fatty liver, increased serum liver enzymes, and hyperplastic nodules. Additionally, PFOA caused hepatocellular adenomas in chronically exposed male rats in the study conducted by Biegel et al. (2001). Although these tumors were not reported to be increased in males rats in the earlier chronic study (Sibinski, 1987), Butenhoff et al. (2012) noted that these lesions represent a regenerative process and that diagnostic criteria for hepatic hyperplastic nodules have changed since the livers from the study were evaluated in 1986.

Increased relative liver weight in mice can result either from *in utero* exposure during the prenatal period or from lactational exposure during the neonatal period (Wolf et al., 2007; White et al., 2009). In other studies, ultrastructural and/or histopathological changes indicative of liver toxicity persisted until adulthood (age 3 months, Quist et al., 2015; age 18 months, Filgo et al., 2015) in offspring of dams dosed with PFOA during gestation. Hepatocellular hypertrophy and periportal inflammation occurred at doses below those that caused increased liver weight (Quist et al., 2015). It is not known whether these sensitive hepatic effects resulted from *in utero* exposure, lactational exposure, or both. Additionally, results from offspring at age 18 months suggest the possibility of an increased incidence of liver tumors from developmental exposures to PFOA, although the study was not designed as a carcinogenicity bioassay (Filgo et al., 2015). Although data from these studies are not amenable dose-response modeling, they support the conclusions that liver toxicity is a sensitive endpoint for PFOA, that the developmental period is a sensitive lifestage for PFOA's hepatic effects, and that increased relative liver weight is a relevant and appropriate endpoint for PFOA's toxicity.

Selection of study and data for dose-response modeling of increased liver weight

Increased relative liver weight has been observed in many studies of PFOA in both rodents and non-human primates. The five publications reporting studies of relative liver weight that were considered for dose-response modeling are summarized in the first part of Table 10 of the <u>Animal Toxicology</u> section. Studies were included if they provide serum PFOA data from the end of the dosing period, and, for rodent studies, include relatively low doses (1 mg/kg/day or less). Rodent studies that meet these criteria were reported in four publications. The 90-day cynomolgus monkey study in which the lowest dose was 3 mg/kg/day is also included in Table 10 of the <u>Animal Toxicology</u> section for comparison purposes, since it used a non-human primate species and has been the focus of risk assessments by other groups.

The 90 day cynomolgus monkey study (Thomford et al., 2001b; Butenhoff et al., 2002) was not considered appropriate for dose-response modeling for several reasons (discussed in detail in Appendix 3). The study does

not provide serum PFOA data that can be used for dose-response modeling because serum PFOA levels did not differ at the two lower doses (3 and 10 mg/kg/day); the high dose (30/20 mg/kg/day) group is excluded for use in dose-response modeling due to overt toxicity. Additionally, the death of one of four animals in the low dose group may have been due to PFOA toxicity. Aside from its lack of utility for dose-response modeling, this study provides no indication of the NOAEL for PFOA toxicity in this species because of the lack of a relationship between administered or internal dose and response, and because of the possibility of overt toxicity at the lowest dose.

Two of the four rodent studies (Loveless et al., 2006; Perkins et al., 2004) used adult male rats, and one of these (Loveless et al., 2006), also used adult male mice. Loveless et al. (2006) administered three different isomeric mixtures of PFOA (linear/branched, linear, and branched) to adult male mice and rats for 2 weeks, while Perkins et al. administered PFOA to adult male rats for 4, 7, or 13 weeks.

As discussed in the <u>Toxicology</u> section, increased relative liver weight associated with hepatocellular hypertrophy is an early manifestation of PFOA's hepatic toxicity. This effect does not appear to increase in magnitude over time, but rather it appears to progress over time to other more severe hepatic effects (Butenhoff et al., 2012). Relative liver weight data from male CD-1 mice after 14 day exposures (Loveless et al., 2006) and 29 day exposures (Loveless et al., 2008) were compared based on administered dose, as Loveless et al. (2008) does not provide serum PFOA levels. This comparison shows that the dose-response curves for increased relative liver weight are similar for the 14 day and 29 day exposure periods. Furthermore, dose-response curves for relative liver weight in male rats were similar after 4, 7, and 13 week exposures (Perkins et al., 2004).

Two additional developmental studies in mice (Lau et al., 2006; Macon et al., 2011) also met the criteria for inclusion in Table 10 of the <u>Toxicology</u> section. Lau et al. (2006) evaluated increased liver weight on GD 18 in pregnant mice dosed with PFOA on GD 1-18. The data for liver weight and serum PFOA levels in pregnant mice in this publication are not presented in a form that is appropriate for dose-response modeling of increased relative liver weight. Data on absolute liver weight and serum PFOA levels are presented in graphical form in the publication; numerical data for absolute liver weight, and liver weight relative to body weight minus weight of gravid uterus, were obtained from the investigator.

Macon et al. (2011) evaluated relative liver weight on PND 1 in female offspring exposed *in utero* on GD 10-17. Comparison of serum PFOA level LOAELs for increased relative liver weight in neonatal female mice in Macon et al. (2011) and in adult male mice (Loveless et al., 2006) suggest similar sensitivity to this effect at both life stages.

The relative liver weight data from male mice exposed to branched/linear PFOA for 14 days (Loveless et al., 2006) were selected for dose-response modeling. These data are shown in Table 17. The branched/linear isomeric mixture is relevant to environmental contamination and human exposure, and almost all toxicological studies of PFOA used the branched/linear isomeric mixture. An increasing response with dose was observed in mice for increased relative liver weight from branched/linear PFOA over the range of doses used in this study. Data from both the standard strain and PPAR-alpha null strains of mice demonstrate that increased liver weight and other types of hepatic toxicity occur through both PPAR-alpha dependent and independent modes of action in mice, and these effects are considered relevant to humans. As shown in Figure 13 in the <u>Mode of Action</u>

section, increased liver weight was not correlated with PPAR-alpha activity in mice in Loveless et al. (2006). As discussed above, relative liver weight does not appear to increase in magnitude with longer exposure durations. Therefore, 14 days is considered to be of sufficient duration, particularly since dose-response modeling is based on serum PFOA level, rather than administered dose, thus avoiding uncertainties about whether internal dose increases with exposures longer than 14 days.

Table 17: Serum PFC CD-1 mice dosed wit (Loveless et al., 2006	OA and relative live h branched/linear P)	er weight in Male FOA for <mark>1</mark> 4 days
Dose (mg/kg/day)	Serum PFOA (µg/ml)	Relative Liver Weight (g/100 g)
0	0.04±0.02	5.14±0.27
0.3	10±1.4	6.12±0.25
1	27±5.0	7.92±0.49
3	66±8.6	10.72±0.63
10	190±29	16.27±1.05
30	241±28	18.28±1.57

Determination of Point of Departure (POD) for increased relative liver weight

USEPA Benchmark Dose Modeling Software 2.6.0.88 was used to perform BMD modeling of the data on increased relative liver weight in male mice exposed to linear/branched PFOA from Loveless et al. (2006). BMD and BMDL serum levels were determined for a BMR of a 10% increase in mean relative liver weight from the control values. All models for continuous data included in the software were run.

Results of the BMD modeling are shown in Table 18, and a more detailed explanation and the complete output of the BMDS software for each model are presented in Appendix 7. Both of the exponential models (models 4 and 5) gave identical fits. These exponential models and the 3rd

degree polynomial model gave acceptable fits to these data. The 3rd degree polynomial model over-fits the data at the high dose, forcing a fit and resulting in a biologically unlikely fit in this area of the dose-response curve. However, the fit of the 3rd degree polynomial model at the lower doses (i.e., in the range of the BMD) is regular and biologically appropriate. It is unlikely that the forced fit at the high dose has any significant influence on the fit of the model at the BMD. Although the 3rd degree polynomial model gave a slightly better fit than the exponential models and also yielded a slightly lower BMDL, the exponential models produced a highly comparable fit and a similar BMDL. As neither model appears to have a claim to greater biological significance, it was recommended that the point-of-departure be derived as the average of the BMDLs for both of these models. **This yielded an average BMDL of 4,351 ng/ml**.

Table 18.	Benchmark	Dose analysis	for a 10%	increase i	n relative liv	er weight from
linear/bran	nched PFOA	in male mice	(Loveless	et al., 200	6) ^a	1.4.1.1.1.1.1. 7 .1.1.1.1.4.9.1.1.

Model	Chi-square p-value ^b	AIC	BMD (Serum PFOA, ng/ml)	BMDL (Serum PFOA, ng/ml)
Exponential (Models 4 and 5)	0.2636	2.12782	4,904 ^d	4,466 ^d
Hill		-		-
Linear	4	-	12	-
Polynomial (2 nd degree)	0.03245 *	6.92134	5,317	4,896
Polynomial (3 rd degree)	0.4678	1.66669	4,682 ^d	4,236 ^d
Average of Exponential (Models 4 and 5) and Polynomial (3rd degree)			4,793	4,351

* Results are shown for all models that gave an acceptable visual fit.

^b A larger Chi-square p-value indicates a better fit to the data.

^e AIC: A measure of information loss from a dose-response model that can be used to compare a specified set of models. The AIC is defined as -2 × (LL - p), where LL is the log-likelihood of the

model given the data, and p is the number of parameters estimated in the model. When comparing models, a lower AIC is preferable to a higher one (USEPA, 2012a).

^dBMDs and BMDLs from the models used to derive the point of departure, as discussed in text.

Application of uncertainty factors for increased relative liver weight

The choice of UFs is consistent with current USEPA IRIS guidance (USEPA, 2012c) and previous risk assessments developed by NJDEP and the DWQI.

The BMDL of 4,351 ng/ml was used as the POD for RfD development. UFs were applied to the POD serum level of 4,351 ng/ml to obtain the Target Human Serum Level. The Target Human Serum level (ng/ml serum) is analogous to the RfD but is expressed in terms of internal, rather than administered, dose.

The total of the UFs applied to the POD serum level was 300, and included the following factors:

- 10 UF for <u>human variation</u>, to account for variation in susceptibility across the human population and the possibility that the available data may not be representative of individuals who are most sensitive to the effect.
- 3 UF for <u>animal-to-human extrapolation</u>, to account for toxicodynamic differences between humans and mice.

The typical uncertainty factor of 3 for toxicokinetic variability between species is not included because the risk assessment is based on comparison of internal dose (serum levels) rather than administered dose.

1 - UF for LOAEL to NOAEL.

The point of departure is a BMDL, not a LOAEL. Therefore, an adjustment for use of a LOAEL is not necessary.

1 - UF for duration of exposure.

The POD is based on increased liver weight resulting from exposure for 2 weeks, while the Healthbased MCL is intended to protect for chronic exposure. However, increased liver weight, usually associated with hepatocellular hypertrophy, is an early manifestation of PFOA's hepatic toxicity. Data from the relevant studies (reviewed above) indicate that the dose-response for this effect, on an internal dose (serum PFOA level) basis, is similar after 2 weeks of exposure and from longer exposures, and that this effect does not appear to occur at lower internal doses (serum PFOA levels) or increase in magnitude with chronic exposures. Rather, the initial effect (increased liver weight accompanied by hepatocellular hypertrophy) appears to progress over time to other more severe hepatic types of effects. Therefore, an adjustment based on duration of exposure is not necessary.

10 - UF for more sensitive effects that are not otherwise considered (e.g. incomplete database).

USEPA IRIS guidance (USEPA, 2012c) states that: "If an incomplete database raises concern that further studies might identify a more sensitive effect, organ system, or lifestage, the assessment may apply a database uncertainty factor." Adverse effects on mammary gland development occur at doses much more than 10-fold lower than those that cause increased relative liver weight. Additionally, hepatic toxicity not associated with increased liver weight occurs at similarly low doses after developmental exposures. Therefore, a UF of 10 to account for more sensitive effects was applied.

The target human serum level is: $\frac{4351 \text{ ng/ml}}{300}$ = 14.5 ng/ml (14,500 ng/L)

Development of Reference Dose for increased relative liver weight

As above, the clearance factor (1.4 x 10⁴ L/kg/day; USEPA, 2016a) was used to derive the RfD from the Target Human Serum Level. This factor was used to develop the RfD that is the basis for the recommended Healthbased MCL. As discussed in the <u>Toxicokinetics</u> section, the clearance factor is consistent with empirical data on the serum:drinking water ratio from communities with contaminated drinking water. It should be noted that health-based drinking water values may also be developed from target human serum levels for PFOA and other PFCs using an approach based on this ratio.

14,500 ng/L x 1.4 x 10⁻⁴ L/kg/day = 2 ng/kg/day

Where: 14,500 ng/L = Target Human Serum Concentration 1.4 x 10⁻⁴ L/kg/day = Clearance Factor 2 ng/kg/day = RfD

Relative Source Contribution factor

A Relative Source Contribution (RSC) factor that accounts for non-drinking water sources including food, soil, air, water, and consumer products is used in the development of health-based drinking water concentrations based on non-carcinogenic effects. An RSC is used by the DWQI for Health-based MCLs, by USEPA for Maximum Contaminant Level Goals, and by other states in development of similar health-based drinking water values. The RSC is intended to prevent total exposure from all sources from exceeding the RfD (USEPA, 2000). When sufficient chemical-specific information on non-drinking water exposures is not available, a default RSC of 0.2 (20%) is used. This default value assumes that 20% of exposure comes from drinking water and 80% from other sources (USEPA, 2000). When sufficient chemical-specific RSC may be derived, with floor and ceiling RSC values of 20% and 80% (USEPA, 2000).

The Health Effects Subcommittee concluded that there are insufficient data to develop a chemical-specific RSC for PFOA. There are no New Jersey-specific biomonitoring data for PFOA, and its frequent occurrence in NJ PWS suggests that New Jersey residents may also have higher exposure from non-drinking sources than the U.S. general population (e.g. NHANES). Elevated levels of PFOA were detected in PWS located throughout NJ in USEPA UCMR3 and other monitoring studies; PFOA was detected much more frequently at > 20 ng/L in NJ PWS (10.5%) than nationwide (1.9%) in UCMR3 (discussed in the Drinking Water Occurrence section). Potential sources of this contamination have been identified in some instances, while sources are unknown in other locations. Environmental contamination with PFOA that results in its presence in drinking water can arise from a number of different types of sources (reviewed in Fate and Transport Relevant to Drinking Water Contamination). These include releases to air, soil, and water from fluoropolymer telomer manufacturing facilities, on-site and off-site disposal from smaller industrial facilities that make products from fluoropolymer dispersions containing PFOA, releases of aqueous firefighting foams, and land application of biosolids from wastewater treatment plants treating waste containing PFOA, among others. These various sources may potentially result in human exposures through contamination of nearby soils, house dust, or other environmental media. In communities with drinking water contamination, consumption of produce from home gardens or grown locally was associated with higher serum levels of PFOA (Emmett et al., 2006a; Holzer et al., 2008; Steenland et al., 2009a).

The exposure factors used to develop the Health-based MCL (below) are based on an adult drinking water consumption rate and body weight. The default RSC of 20%, while not explicitly intended for this purpose, also partially accounts for the higher PFOA exposures in infants. Exposures to infants, both breastfed and consuming formula prepared with contaminated drinking water, are much higher than in than older individuals. Infants consume much more fluid (breast milk or formula) than older individuals on a body weight basis; about 10-fold more from birth to 1 month of age, and 4 -6 fold more between ages 6-12 months. Additionally, PFOA concentrations in breast milk are similar or higher than in the mother's drinking water source (Post et al., 2012).

For these reasons, although serum levels in infants are similar to their mother's at birth (Post et al., 2012), they increase rapidly by several-fold shortly after birth for a period of at least several months. As shown in Figure 16, this increase was five-fold or greater in a considerable portion of infants evaluated in two studies (Fromme et al., 2010; Mogensen et al., 2015). Additionally, Monte Carlo simulations of results of a pharmacokinetic model predict median, 95th percentile, and maximum infant:mother plasma PFOA ratios of 4.5-fold, 7.8-fold,



and 15.3-fold, respectively, during the period of greatest infant exposure (Verner et al., 2016a; Figure 17).

Figure 16. Changes in PFOA levels in breast-fed infants from birth to later timepoints (Fromme et al., 2010; Mogensen et al., 2015)



Figure 17. Monte Carlo simulations of child/mother ratios of plasma PFOA levels (ng/ml) a breastfeeding period of 30 months. Black line - 50th percentile; blue line - 5th percentile; red line - 95th percentile; dotted lines - minimum and maximum values (Verner et al., 2016).

These higher infant exposures must be considered because the toxicological effects of concern (delayed mammary gland development and increased relative liver weight) occur from short term exposures relevant to elevated exposures in infancy. Cross-fostering studies (discussed in Toxicology section) show that lactational exposure causes increased relative liver weight and delayed mammary gland development (White et al., 2007; White et al., 2009) in animals with no *in utero* exposure. Additionally, hepatic toxicity that persists until adulthood occurs in offspring of dams exposed to low doses of PFOA during gestation (Quist et al., 2015). These effects could result from prenatal or lactational exposure, or both.

For the reasons discussed above, the default RSC of 20% is used to develop the Health-based MCL.

Development of potential Health-based MCL based on hepatic effects

 $\frac{2 \text{ ng/kg/day x 70 kg x 0.2}}{2 \text{ L/day}} = \frac{14 \text{ ng/L}}{(0.014 \text{ µg/L})}$

Where:

2 ng/kg/day = Reference Dose 70 kg = assumed adult body weight 0.2 = Relative Source Contribution from drinking water 2 L/day = assumed adult daily drinking water intake

List of Abbreviations and Acronyms Frequently Used in New York State Human Health Fact Sheets.

1 x 10 ⁻⁶	one-in-one million
ACPF	adjusted cancer potency factor
ADAF	age-dependent adjustment factor
ADI	acceptable daily intake
adj	adjusted
AIC	Akaike information criterion
ATSDR	Agency for Toxic Substance and Disease Registry
AUC	area under the curve
AWQGV	ambient water quality guidance value
BMC	benchmark concentration
BMCL	benchmark concentration, lower 95% confidence limit
BMD	benchmark dose
BMDL	benchmark dose, lower 95% confidence limit
BMDL ₁₀	BMDL, 10% BMR
BMDL ₅₀	BMDL, 50% BMR
BMDL _{1SD}	BMDL, BMR of one standard deviation
BMDL _{ADJ}	BMDL, adjusted to continuous exposure
BMR	benchmark response
BW	body weight
$BW^{2/3}$	body-weight raised to the 2/3 power scaling
$BW^{3/4}$	body-weight raised to the 3/4 power scaling
CA EPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CL	confidence limit
CNS	central nervous system
CPF	cancer potency factor
DAF	dosimetric adjustment factor
DNA	deoxyribonucleic acid
DWCR	drinking water consumption rate
EFSA	European Food Safety Authority
F ₁	first filial generation (in experimental animals)
F ₂	second filial generation (in experimental animals)
FAO	Food and Agriculture Organization of the United Nations
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	gram
GD	gestation day
HC	Health Canada
HEC	human equivalent concentration
HED	human equivalent dose
HED _{BMDL10}	human equivalent dose at the $BMDL_{10}$
HEDLOEL	human equivalent dose at the LOEL
HED _{NOEL}	human equivalent dose at the NOEL
HI	hazard index
hr	hour
HSDB	Hazardous Substance Data Bank

IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System, US EPA
kg	kilogram
L	liter
L/day	liters per day
L/kg	liters per kilogram
L/kg-dav	liters per kilogram dav
LADC	lifetime average daily concentration
LADD	lifetime average daily dose
LCL	lower confidence limit
LED	lower bound on effective dose
IFI	lowest-effect level
LDD	lowest-observed-adverse-effect level
LOALL	lowest-observed-effect level
nog	microgram
$m_{2}g/m^{3}$	microgram per oubie motor
meg/m meg/ha dav	micrograms per cubic meter
mcg/kg-day	micrograms per kilogram body weight per day
mcg/L	micrograms per liter
MCL C	maximum contaminant level
MCLG	maximum contaminant level goal
MDPH	Massachusetts Department of Public Health
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
mg/hr	milligrams per hour
mg-hr/L	milligrams-hour per liter
mg/kg-day	milligrams per kilogram body weight per day
mg/kg/day	milligrams per kilogram body weight per day
mg/m ³	milligrams per cubic meter
MLE	maximum likelihood estimate
MOA	mode-of-action
MRL	minimal risk level
MTD	maximum tolerated dose
NAS	National Academy of Sciences
NHANES	National Health and Nutrition Examination Survey
ng	nanogram
ng/L	nanograms per liter
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
NTP	National Toxicology Program
NYS	New York State
NYS DEC	New York State Department of Environmental Conservation
NYS DOH	New York State Department of Health
NYCRR	New York Code of Rules and Regulations
OPP	Office of Pesticide Programs US FPA
P (value)	nrobability value
DRDK	physiologically-based pharmacokinetic
PDAF	physiologically-based phannacokinetic
	pharmacouynamic aujustificitt factor
PB	picogram

pg/L	picograms per liter
PKAF	pharmacokinetic adjustment factor
POC	principal organic contaminant
POD	point-of-departure
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
RfC	reference concentration
RfD	reference dose
RPF	relative potency factor
RR	relative risk
RSC	relative source contribution
SAB	EPA Science Advisory Board
SD	standard deviation
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxicity equivalent
TW	time-weighted
TWA	time-weighted-average
UCL	upper confidence limit
UCMR	Unregulated Contaminant Monitoring Rule, US EPA
UF	uncertainty factor
UOC	unspecified organic contaminant
UR	unit risk
U.S.	United States
US EPA	United States Environmental Protection Agency
WBC	white blood cell
WCAF	water consumption adjustment factor
WHO	World Health Organization
wk	week