

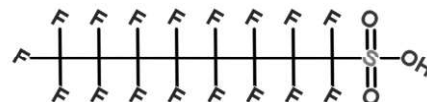
Fact Sheet Date: April 8, 2021

**NEW YORK STATE  
HUMAN HEALTH FACT SHEET**

**Ambient Water Quality Value for  
Protection of Human Health and Sources of Potable Water<sup>1</sup>**

**SUBSTANCE:** Perfluorooctane Sulfonic Acid (PFOS)

**CAS REGISTRY NUMBER:** 1763-23-1



**AMBIENT WATER QUALITY VALUE:** 0.0027 mcg/L

**BASIS:** Oncogenic Effects (6 NYCRR 702.4)

**INTRODUCTION**

Perfluorooctane sulfonic acid (perfluorooctane sulfonate, PFOS) is an environmentally persistent anthropogenic chemical that had many uses such as in fire-fighting foams and fabric stain-resistance treatments. PFOS is no longer manufactured in the United States but can be imported and used for specific limited uses. PFOS is released into the environment from fluoropolymer manufacturing or processing facilities, effluent releases from wastewater treatment plants, landfill leachates, the spreading of biosolids, and the use of aqueous fire-fighting foams (ATSDR, 2018; HC, 2018).

The toxicity of PFOS has been reviewed and summarized by several authoritative bodies (ATSDR, 2018; EFSA CONTAM, 2018; HC, 2018; NTP, 2016; NJ DEP, 2019; OECD, 2002; US EPA 2009, 2016a). These reviews identify important studies on the health effects associated with exposure to PFOS, including studies (when available) on the chronic (oncogenic and nononcogenic), developmental, and reproductive effects observed in humans and animals. We derived the ambient water quality value of 0.0027 mcg/L for PFOS 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.

<sup>1</sup> A list of commonly used abbreviations and acronyms is attached as Exhibit 4.

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

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

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

Epidemiological studies of workers or the general population have not provided convincing evidence of increased cancer risk from PFOS exposure (ATSDR, 2018; EFSA CONTAM, 2018; US EPA, 2016a). The results of one study in occupationally exposed workers showed an association between PFOS exposure and increased incidence of bladder cancer; however, the results were considered inconclusive due to the limited size of the study cohort (Alexander and Olsen, 2007; CA EPA, 2010; EFSA CONTAM, 2018; OECD, 2002; US EPA 2016a).

There is only one study that evaluates the oncogenicity of PFOS in animals (Butenhoff et al., 2012a; OECD, 2002).<sup>2</sup> In this study, male and female rats were fed diets containing PFOS at concentrations of 0.5, 2, 5, or 20 parts per million (ppm) for 104 weeks.<sup>3</sup> A recovery group was fed diets containing 20 ppm for 52 weeks and was observed until death. PFOS increased the incidence of hepatocellular adenoma/carcinoma in male and female rats at the highest dose (20 ppm), equivalent to 0.984 milligrams per kilogram per day (mg/kg-day) in males and 1.25 mg/kg-day in females. A statistically significant increase in thyroid tumors in male rats in the recovery group was reported at the highest dose tested (0.984 mg/kg-day).<sup>4</sup> PFOS also increased the incidence of mammary tumors in female rats without a clear dose-response effect (Butenhoff et al., 2012a; OECD, 2002)<sup>5</sup>. Based on the results of this study, some agencies consider PFOS to be oncogenic in animals (EFSA, 2008; HC, 2018; NJ DEP, 2019; OECD, 2002).

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<sup>2</sup> This study was conducted by the 3M Company in 2002 and was made publically available via a report by Thomford (2002) prior to publication in Butenhoff et al. (2012a).

<sup>3</sup> These dietary concentrations correspond to oral doses of 0, 0.024, 0.098, 0.242, and 0.984 mg/kg-day in males and 0, 0.029, 0.120, 0.299, and 1.25 mg/kg-day in females.

<sup>4</sup> The authors stated that the “observation of a statistically significant increased incidence of thyroid follicular cell adenoma in the 20 ppm recovery group males without observation of similar increases in males and/or females of the 20 ppm group is paradoxical and may represent a chance occurrence.”

<sup>5</sup> Females had a statistically significant increase in follicular cell adenoma/carcinoma, but only at the 5-ppm dose level.

In determining whether PFOS has oncogenic effects under 6 NYCRR 700.1, we also considered oncogenicity data for a structurally similar compound, perfluorooctanoic acid (PFOA). PFOS and PFOA share similar physical and chemical properties (ATSDR, 2018; US EPA, 2016a) and are frequently found together in the environment (Kannan et al., 2005). Studies show that PFOS and PFOA are readily absorbed after oral exposure, are not metabolized in the body, and accumulate primarily in the serum, kidney, and liver. In addition, both compounds have long serum half-lives in humans, generally ranging from about 2 to 4 years for PFOA and about 4 to 6 years for PFOS (ATSDR, 2018; Olsen et al., 2007; US EPA, 2016a). PFOA and PFOS are found in humans bound to blood serum albumin (Salvalaglio et al., 2010). PFOA (Butenhoff et al., 2012b) and PFOS (Butenhoff et al., 2012a) caused liver adenomas and carcinomas in dietary studies in rodents. 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)(vi), based on induction of tumors in one mammalian species, reported in two independent studies (NYS, 2019). Thus, PFOS has oncogenic effects as defined under 6 NYCRR 700.1 because it induces tumors in “one mammalian species, supported by positive results for another substance for which similar oncogenic effects are anticipated because of similarity of functional groups or metabolic or toxicologic pathways.”

Most of the evidence from short-term *in vitro* assays suggest that PFOS is not active in short-term tests indicative of oncogenic potential (ATSDR, 2018; EFSA, 2008; HC, 2018; OECD, 2002; US EPA, 2016a). However, some studies have shown limited positive evidence of PFOS having direct interaction with DNA, such as adduct formation in calf thymus DNA (Lu et al., 2012) as well as DNA damage (comet assay) and micronucleus formation in rat bone marrow (Celik et al., 2013).

It has been hypothesized that the tumors observed after dietary exposure of rats to PFOS may be due to activation of nuclear peroxisomal proliferator activated receptors (PPAR)<sup>6</sup> and other nuclear receptors (Butenhoff et al., 2012a; Jacquet et al., 2012). However, it has also been suggested that other, PPAR-independent mechanisms may be involved in PFOS carcinogenesis (EFSA CONTAM, 2018). Since the oncogenic MOA for PFOS is unknown<sup>7</sup>, under 6 NYCRR 702.4, “the standard or guidance value shall be based

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<sup>6</sup> PPAR $\alpha$  regulates lipid homeostasis by altering the expression of genes involved in uptake, activation, and oxidation of fatty acids (Butenhoff et al., 2012a; Elcombe et al., 2012).

<sup>7</sup> US EPA (2005a) 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 PFOS is unknown, and the available data do not suggest that PFOS acts through a mutagenic MOA, ADAFs were not used in the derivation of potential ambient water quality values for PFOS (oncogenic effects).

on the 95 percent lower confidence limit on the human dose corresponding to an excess lifetime cancer risk of one-in-one million.”

The New Jersey Department of Environmental Protection (NJ DWQI, 2018; NJ DEP, 2019)<sup>8</sup> evaluated the available scientific literature on the oncogenic effects of PFOS and derived a CPF for PFOS<sup>9</sup> based on the dose-response data for liver tumors in rats (Tables 1 and 3) reported in Butenhoff et al. (2012a). The NJ DEP used area under the curve calculations to obtain a time weighted average PFOS serum concentration for each administered dose (including the recovery group), and then modeled a serum BMDL<sub>10</sub> in female rats (137 mg/L), which was used as the POD.<sup>10</sup> Linear extrapolation from the POD yielded a rat CPF (expressed as the risk per unit of serum concentration) of 0.00073 (mg/L)<sup>-1</sup>. The NJ DEP obtained the corresponding human cancer potency factor (9.0 (mg/kg-day)<sup>-1</sup>) for PFOS using the same human one-compartment model the US EPA used to derive a PFOS reference dose (2016a).<sup>11</sup>

We derived a potential ambient water quality value (oncogenic effects) for PFOS based on the dose-response data for liver tumors in rats reported in Butenhoff et al. (2012a) using the time-weighted average (area under the curve) PFOS serum concentrations reported in NJ DEP (2019).<sup>12</sup> We did not include recovery groups in the dose-response modeling because the duration of exposure differed between animals in the recovery group and animals in the other dose groups. Animals in the recovery groups were exposed to PFOS via the diet for 52 weeks and were given a control diet (without PFOS) for the remainder of the 104 week study. Whereas, animals in the other dose groups were exposed to PFOS for the entire duration of the study. Based on the range of observation for liver tumor incidence reported in the Butenhoff et al. (2012a) study, we selected a BMR of

<sup>8</sup> 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, 2018).

<sup>9</sup> No other cancer potency factors for PFOS derived by authoritative bodies were located. Health Canada (2018) evaluated the oncogenic effects of PFOS and derived a tolerable daily intake (i.e., reference dose) based on the increased incidence of hepatocellular tumors in male rats. Health Canada stated that “Although the mode of action for PFOS-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOS is a non-mutagenic compound. For this reason, a non-linear low-dose extrapolation approach (i.e., the tolerable daily intake (TDI) approach) is the most appropriate method for deriving a health-based value (HBV) for cancer.” However, under 6 NYCRR 702.4, if “data on mode-of-action are unavailable, or if the mode-of-action analysis provides evidence of linearity at low doses or does not provide unequivocal evidence of nonlinearity at low doses, 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.” Therefore, Health Canada’s tolerable daily intake was not further considered as a potential basis for an ambient water quality value for PFOS based on oncogenic effects.

<sup>10</sup> A BMDL<sub>10</sub> is the 95% LCL on the benchmark serum level (internal dose) associated with a 10% increase in liver tumors.

<sup>11</sup> Cancer potency factor = Risk per unit serum level / Clearance = 0.00073 (mg/L)<sup>-1</sup> / 0.000081 L/kg-day = 9.0 (mg/kg/day)<sup>-1</sup>. PFOS clearance (US EPA, 2016a) = (ln2/PFOS half-life) x volume of distribution = (0.693/1971 days) x 0.23 L/kg = 0.000081 L/kg-day.

<sup>12</sup> Serum PFOS data were obtained from Tables 45 and 46 of NJ DEP (2019).

5% for dose-response modeling and chose the serum BMDL<sub>05</sub> as the POD<sup>13</sup>, which is consistent with 6 NYCRR 702.4 and US EPA (2012a) guidance. We obtained serum BMDL<sub>05</sub> estimates based on liver tumors in male rats and female rats using the cancer multistage model (Tables 1 and 2). We did not consider alternate models because the multistage model adequately described the dose-response data within the range of observation (Table 2).<sup>14</sup> This is consistent with 6 NYCRR 702.4 and recent U.S. Environmental Protection Agency's cancer risk-assessment guidance and practice giving preference (among models that adequately described the data) to the multistage model when modeling cancer bioassay data (Gehlhaus et al., 2011; US EPA, 2005b, 2012a,b).<sup>15</sup>

Experimental evidence to indicate that one sex is a better surrogate for humans was not found, and our serum BMDL<sub>05</sub> estimates (i.e., 33,761 mcg/L for males and 62,453 mcg/L for females) differed by only about 2-fold. Thus, we selected the median serum BMDL<sub>05</sub> (48,107 mcg/L) as the POD and the basis of a potential ambient water quality value (oncogenic effects) for PFOS.

Using procedures consistent with those outlined in 6 NYCRR 702.4, we calculated the HED at the median serum BMDL<sub>05</sub> (48,107 mcg/L) using a human single-compartment model to obtain a pharmacokinetic adjustment factor (NJ DEP, 2019; US EPA, 2016a) that accounts for the large interspecies differences in PFOS serum half-lives observed in studies of humans and animals.

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<sup>13</sup> A BMDL<sub>05</sub> is the 95% LCL on the benchmark (internal) dose associated with a 5% increase (relative to controls) of an effect. A BMDL is also known as an LED, which is the 95 percent lower confidence limit on the effective dose as described in 6 NYCRR 702.4.

<sup>14</sup> Dose-response curves were also visually inspected to ensure that the model adequately describes the data.

<sup>15</sup> 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."

$$\text{HED}_{\text{BMDL05}} = \text{serum BMDL}_{05} \times \text{PKAF} \times \text{PDAF}$$

where,

$$\text{median serum BMDL}_{05} = 48,107 \text{ mcg/L}$$

$$\text{PKAF} = \text{Pharmacokinetic Adjustment Factor} = 8.1 \times 10^{-5} \text{ L/kg-day}^*$$

$$\text{PDAF} = \text{Pharmacodynamic Adjustment Factor} = 1^{**}$$

$$\text{HED}_{\text{BMDL05}} = 48,107 \text{ mcg/L} \times 8.1 \times 10^{-5} \text{ L/kg-day} \times 1$$

$$\text{HED}_{\text{BMDL05}} = 3.9 \text{ mcg/kg-day (or } 3.9 \times 10^{-3} \text{ mg/kg-day)}$$

$$*\text{PKAF} = \text{CL}_{\text{human}}$$

where,

$\text{CL}_{\text{human}} = \text{Volume of Distribution} \times (\ln 2 \div \text{half-life})$ , assuming first-order kinetics.

$\text{CL}_{\text{human}} = 0.23 \text{ L/kg} \times (0.693 \div 1971 \text{ days}) = 0.000081 \text{ L/kg-day}$  (US EPA, 2016a)

\*\*Based on evidence and analysis in US EPA (1992), we assumed that in the absence of evidence to the contrary, animals and humans are at equal lifetime excess cancer risk at equal lifetime internal doses. Therefore, the adjustment factor for pharmacodynamic differences is one.

We divided the  $\text{HED}_{\text{BMDL05}}$  by 50,000 to obtain the human risk-specific dose corresponding to the 95% LCL on the dose ( $7.8 \times 10^{-5} \text{ mcg/kg-day}$ ) associated with an excess lifetime oncogenic cancer risk of one-in-one-million.<sup>16</sup> We selected this dose for use in the derivation of a potential ambient water quality value (oncogenic effects) for PFOS.

$$\text{Human risk-specific } 1 \times 10^{-6} \text{ Dose} = \text{HED}_{\text{BMDL05}} / 50,000$$

$$\text{Human risk-specific } 1 \times 10^{-6} \text{ Dose} = 3.9 \text{ mcg/kg-day} / 50,000$$

$$\text{Human risk-specific } 1 \times 10^{-6} \text{ Dose} = 7.8 \times 10^{-5} \text{ mcg/kg-day}$$

Using procedures that are consistent with 6 NYCRR 702.2 and 702.4, we calculated the PFOS water concentration (0.0027 mcg/L, two significant figures) corresponding to an excess lifetime cancer risk of one-in-one million using the risk-specific ( $1 \times 10^{-6}$ ) human dose ( $7.8 \times 10^{-5} \text{ mcg/kg-day}$ ) assuming a 70-kg adult

<sup>16</sup> A dose at any lifetime excess cancer risk can be obtained from the straight line that extrapolates 5% excess lifetime cancer risk at the  $\text{HED}_{\text{BMDL05}}$  to zero excess risk at zero dose. For example, a one-in-one-million excess lifetime risk (equal to 0.000001) is 50,000-fold lower than an excess lifetime risk of 5% (equal to 0.05). Therefore, the dose at a one-in-one-million excess lifetime risk is obtained by dividing the dose at a 5% excess risk by 50,000 (equal to  $0.05/0.000001$ ).

consumes 2 liters of water per day. We selected 0.0027 mcg/L as the potential ambient water quality guidance value (oncogenic effects) for PFOS.

$$\text{Risk-Specific (1 x 10}^{-6}\text{) Water Concentration} = \frac{\text{Risk Specific (1 x 10}^{-6}\text{)Dose x Body Weight}}{\text{Drinking Water Consumption Rate}}$$

$$1 \times 10^{-6} \text{ Water Concentration} = \frac{7.8 \times 10^{-5} \text{ mcg/kg-day} \times 70 \text{ kg}}{2\text{L/day}}$$

$$1 \times 10^{-6} \text{ Water Concentration} = 0.0027 \text{ mcg/L}$$

## 702.5. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON NONONCOGENIC EFFECTS

Human studies on PFOS have suggested possible links between exposure to PFOS and effects on immune response, cholesterol, birth weight, and various thyroid parameters (ATSDR, 2018; EFSA CONTAM, 2018; NTP, 2016; US EPA, 2016a). These studies are inadequate for use in dose-response assessment, due to lack of reliable quantitative exposure data (US EPA, 2016a).

The US EPA (2016a), the Minnesota Department of Health (MDH, 2019), and the NJ DEP (NJ DWQI, 2018; NJ DEP, 2019) evaluated the available animal and human studies on the nononcogenic effects of PFOS, and derived RfDs and health based-values for PFOS in drinking water based on effects observed in animals (Table 4).

The US EPA (2016a) based its RfD on developmental toxicity (reduced pup body weight) in the offspring of rats exposed to PFOS for 84 days across two generations (see Exhibit 1). The US EPA converted the NOEL of 0.1 mg/kg-day to a serum PFOS level of 6.26 mg/L using the rodent pharmacokinetic model of Wambaugh et al. (2013), and then applied a human single compartment model to obtain the corresponding human POD (i.e., an HED<sub>NOEL</sub> of 0.00051 mg/kg-day).<sup>17</sup> Application of a total uncertainty factor of 30 (10X for intraspecies differences and 3X for interspecies pharmacodynamic differences) yielded the RfD of 2.0 x 10<sup>-5</sup> mg/kg-day.

<sup>17</sup> Human equivalent dose (HED<sub>NOEL</sub>) = PFOS serum concentration x PFOS clearance = 6.26 mg/L x 0.000081 L/kg-day = 0.00051 mg/kg-day. Where, PFOS clearance = (ln2/PFOS half-life) x volume of distribution = (0.693/1971 days) x 0.23 L/kg = 0.000081 L/kg-day

The MDH (2019) based its RfD on immune effects (increased interleukin 4 and decreased sheep red blood cell-specific IgM levels) in adult male mice exposed to PFOS for 60 days (see Exhibit 2). The MDH converted the measured serum PFOS level of 2.36 mg/L (corresponding to the administered dose NOEL of 0.0167 mg/kg-day) to obtain the human point of departure (an  $HED_{NOEL} = 0.000307$  mg/kg-day)<sup>18</sup> using a single-compartment model based on a human clearance calculated with a shorter assumed mean half-life than was used by the US EPA (3.4 years [Li et al., 2018] compared to 5.4 years [Olsen et al., 2007]). Application of a total UF of 100 (10 for intraspecies differences, 3 for interspecies pharmacodynamic differences, and 3 for database uncertainty) yielded an RfD of  $3.1 \times 10^{-6}$  mg/kg-day.

The NJ DEP (NJ DWQI, 2018; NJ DEP, 2019) derived an RfD ( $2 \times 10^{-6}$  mg/kg-day) based on immune effects (decreased plaque forming cell response) in adult male mice exposed to PFOS for 60 days (see Exhibit 3). In this study, the NOEL for immune effects is 0.0083 mg/kg-day, corresponding to a measured serum PFOS level of 0.674 mg/L, and the LOEL for these effects is 0.083 mg/kg-day (which corresponds to a PFOS serum concentration of 7.132 mg/L). The NJ DEP used the measured PFOS serum level at the NOEL as the point of departure and applied a UF of 30 (10X for intraspecies differences and 3X for interspecies pharmacodynamic differences) to obtain a target human serum level of 0.0225 mg/L. The NJ DEP calculated the RfD from the target human serum level using the same human single-compartment model used by the US EPA (2016a).<sup>19</sup>

Using procedures consistent with 6 NYCRR 702.5, we selected the POD used by the NJ DEP (NJ DWQI, 2018; NJ DEP, 2019) as the basis of a potential ambient water quality value (nononcogenic effects) for PFOS. The primary considerations for selecting this POD were:

- The LOEL for immune effects in the study selected by the NJ DEP (0.083 mg/kg-day) is lower than the LOEL for developmental toxicity (0.4 mg/kg-day) in the study used by the US EPA.
- Immunotoxicity is a well-established and sensitive endpoint for PFOS in animals. In addition, epidemiological studies have reported associations between serum PFOS levels and immunotoxicity (Grandjean et al., 2012; Granum, 2013; Stein et al., 2016).

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<sup>18</sup> Human equivalent dose ( $HED_{NOEL}$ ) = PFOS serum concentration x PFOS clearance = 2.36 mg/L x 0.00013 L/kg-day = 0.000307 mg/kg-day. Where, PFOS clearance =  $(\ln 2 / \text{PFOS half-life}) \times \text{volume of distribution} = (0.693 / 1241 \text{ days}) \times 0.23 \text{ L/kg} = 0.00013 \text{ L/kg-day}$

<sup>19</sup> Clearance factor is from US EPA (2016a). RfD = PFOS target human serum level x PFOS clearance = 0.0225 mg/L x 0.000081 L/kg-day =  $2 \times 10^{-6}$  mg/kg-day.



- A recent major report on PFOS immunotoxicity by the National Toxicology Program (2016) which evaluated animal, human and *in vitro*/mechanistic studies concluded that PFOS is presumed to be an immune hazard to humans.

The NJ DEP derived their RfD using a measured PFOS serum level at the NOEL of 0.674 mg/L as the rat POD. Consistent with 6 NYCRR 702.5, this POD is expressed as a HED of 0.000055 mg/kg-day by applying the human single-compartment model used by the US EPA (2016a) to the measured PFOS serum level.<sup>20</sup> The total UF of 30 applied by the NJ DEP is consistent with 6 NYCRR 702.5 given the areas of uncertainty and variation.

$$\text{RfD} = \text{HED}_{\text{NOEL}} / \text{UF}$$

where,

$$\text{UF} = 30 \text{ (3X for interspecies differences in pharmacodynamics, 10X for inter-human variability)}$$

$$\text{RfD} = 0.000055 \text{ mg/kg-day} / 30$$

$$\text{RfD} = 1.8 \times 10^{-6} \text{ mg/kg-day or } 0.0018 \text{ mcg/kg-day}$$

We applied the procedure outlined in 6 NYCRR 702.2 and 702.5 to derive a potential ambient water quality value for noncogenic effects (0.013 mcg/L, rounded to two significant figures) using the selected RfD (0.0018 mcg/kg-day), a 20% relative source contribution (0.2), and assuming an adult body weight of 70 kg and a drinking-water consumption rate of 2 L/day.

$$\text{Potential Ambient Water Quality Value} = \frac{0.0018 \text{ mcg/kg-day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/kg-day}} = 0.013 \text{ mcg/L}$$

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 noncogenic effects of PFOS was considered, but was not used because the weight of scientific evidence is insufficient to conclude that exposure to PFOS during childhood poses a greater risk of noncogenic effects than exposure during adulthood (ATSDR, 2018, OECD, 2002). In addition, for the toxicological endpoint on which the ambient water quality value (noncogenic effects) is based (immune toxicity), effects were observed at a lower PFOS exposure level in adult animals (Dong et al.,

<sup>20</sup> Human equivalent dose ( $\text{HED}_{\text{NOEL}}$ ) = PFOS serum concentration x PFOS serum clearance = 0.674 mg/L x 0.000081 L/kg-day = 0.000055 mg/kg-day.

2009) than the maternal exposure that caused effects in young animals exposed gestationally (Luebker et al., 2005).

## **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 PFOS 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 0.0027 mcg/L (oncogenic effects) and 0.013 mcg/L (nononcogenic effects) for PFOS. The most stringent of the potential values is 0.0027 mcg/L (6 NYCRR 702.4, Oncogenic Effects) and thus, this value is selected as the ambient water quality value [Health (Water Source)] for PFOS.

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## **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 “PFOS and toxicity”.

Bureau of Toxic Substance Assessment  
New York State Department of Health  
August 2019

## **EXHIBITS**

- Exhibit 1. US EPA (2016a,b) Reference Dose Derivation and Lifetime Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS).
- Exhibit 2. MDH (2019) Derivation of Reference Dose and Health-based Water Value for Perfluorooctane Sulfonate.
- Exhibit 3. NJ DWQI (2018) Health-based MCL for Perfluorooctane Sulfonate.
- Exhibit 4. List of Abbreviations and Acronyms Frequently Used in New York State Human Health Fact Sheets.

**Table 1. Exposure Response Data for Liver Tumors in Male and Female Rats.<sup>A</sup>**

Tumor Site	Tumor Type	PFOS Time-weighted Average Serum Concentrations (mcg/L) and Tumor Incidence				
		25	2,554	11,724	31,225	116,950
rat (male)						
liver	hepatocellular adenoma	0/60	3/50	3/50	1/50	7/60 <sup>B</sup>
rat (female)						
liver	hepatocellular, adenoma/carcinoma combined	0/60	1/50	1/49	1/50	6/60 <sup>B</sup>

<sup>A</sup>Tumor incidence data come from Tables 5 and 6 of the Butenhoff et al. (2012a) study. PFOS serum concentrations for this study are from Tables 45 and 46 of NJ DEP (2019) and are based on the area under the curve serum levels for each dose-group, time-weighted across the duration of the study. NJ DEP (2019) reported serum concentrations in units of ng/mL (which is equivalent to units in mcg/L).

<sup>B</sup>Statistically significant ( $p \leq 0.05$ ) compared to controls.

**Table 2. Results of Benchmark Dose Modeling<sup>A</sup> of Tumor Incidence Data from Butenhoff et al. (2012a).**

Species/ Gender	Tumor Site	BMD <sub>05</sub> <sup>B</sup> (mcg/L)	BMDL <sub>05</sub> <sup>C</sup> (mcg/L)	Chi-Squared p-Value for Goodness-of-Fit <sup>D</sup>
rat (male)	liver	89,108	33,761	0.1873
rat (female)	liver	134,128	62,453	0.5186

<sup>A</sup>Benchmark Dose Software Version 3.4 (US EPA, 2012c); the multistage model is preferred for dose-response modeling of cancer bioassay data (US EPA, 2012a,b); the multistage model was run on default settings (i.e., default parameters including a 2<sup>o</sup> polynomial).

<sup>B</sup>The BMD<sub>05</sub> is the internal dose (PFOS serum concentration) associated with a 5% increase in tumor incidence relative to background (control) incidence.

<sup>C</sup>The BMDL<sub>05</sub> is the 95% LCL on the internal dose (PFOS serum concentration) associated with a 5% increase in tumor incidence relative to background (control) incidence.

<sup>D</sup>The p-value for the Chi-Squared test should be greater than 0.05 given an *a priori* selection of a model (i.e., the cancer multistage) (US EPA, 2012a), which indicates that there is no significant difference between expected (i.e., model predicted) and observed tumor incidences.

**Table 3. Authoritative Body Cancer Potency Estimates for PFOS.<sup>1</sup>**

Agency	Risk-Specific Dose <sup>2</sup> (mg/kg-day)	Cancer Potency Factor (mg/kg-day) <sup>-1</sup>	Extrapolation Methods		Summary
			High to Low Dose	Animal to Human	
NYS (derived under 6 NYCRR 702.4)	$7.8 \times 10^{-8}$	12.8	linearized multistage model with linear extrapolation from the POD	single-compartment human PBPK model	Based on increased incidence of hepatocellular adenomas and carcinomas in male and female rats exposed to PFOS via the diet for two years
NJ DWQI (2018)	$1.1 \times 10^{-7}$	9.0	dose-response models with linear extrapolation from the POD	single-compartment human PBPK model	Based on the combined incidence of hepatocellular adenomas and carcinomas in female rats exposed to PFOS via the diet for two years.
Health Canada (2018)	--	--	uncertainty factors	chemical-specific UF of 10 (pharmacokinetics) <sup>3</sup>	Based on hepatocellular tumors in male rats exposed via the diet for two-years. Using a noncancer threshold approach, Health Canada calculated a TDI of 0.0011 mg/kg-day for carcinogenicity based on weight of evidence that suggests that PFOS is a non-mutagenic compound. The TDI is based on a BMDL <sub>10</sub> of 0.28 mg/kg-day and a total UF of 25 (2.5 for interspecies pharmacodynamics and an intraspecies UF of 10.

<sup>1</sup>US EPA (2016a,b) also evaluated human and animal studies on the carcinogenicity of PFOS and concluded that “there is *Suggestive Evidence of Carcinogenic Potential* of PFOS in humans” based on the liver and thyroid adenomas observed in the Butenhoff et al. (2012a) study. However, US EPA did not derive a cancer potency factor for PFOS. While the Butenhoff et al. (2012a) study reported statistically significant increased incidences of hepatocellular adenomas and carcinomas in male and female rats exposed to PFOS in the highest dose groups, as well as positive statistical trends for both datasets, US EPA (2016b) concluded that “existing evidence does not support a strong correlation between the tumor incidence and dose to justify a quantitative assessment.”

<sup>2</sup>The dose associated with an excess lifetime cancer risk of one-in-one million (i.e.,  $1 \times 10^{-6}$  dose), where,  $1 \times 10^{-6}$  dose =  $1 \times 10^{-6}$ /cancer potency factor.

<sup>3</sup>Health Canada (2018) calculated a chemical specific pharmacokinetic adjustment factor of 10 based on differences in PBPK modeled steady-state plasma PFOS predictions at 0.1 mg/kg-day between humans and rats [i.e., chemical specific UF = human steady state PFOS plasma level (360 micrograms per milliliter (mcg/mL)) ÷ estimated rat steady state PFOS plasma level (36.9 mcg/mL) = 10].



**Table 4. Reference Doses for PFOS Derived by Authoritative Bodies.**

Agency <sup>1</sup>	Reference Dose <sup>2</sup> (mg/kg-day)	Point of Departure		UF	Summary
		Dose (mg/kg-day) or Serum Concentration (mg/L)	Basis		
US EPA (2016a,b)	$2.0 \times 10^{-5}$	6.26 mg/L in serum (rats) HED <sub>NOEL</sub> = 0.00051 mg/kg-day	serum NOEL	30	Based on reduced body weight in offspring of rats exposed by gavage in a two-generation study. UF of 30: 10 for intraspecies differences and 3 for interspecies differences (Exhibit 1).
MDH (2019)	$3.1 \times 10^{-6}$	2.36 mg/L in serum (mice) HED <sub>NOEL</sub> = 0.000307 mg/kg-day	serum NOEL	100	Based on increased interleukin 4 (IL-4) and decreased sheep red blood cell (SRBC) specific IgM levels in adult male mice. UF of 100: 10 for intraspecies differences, 3 for interspecies differences, 3 for database uncertainties (Exhibit 2).
NJ DEP (2019)	$1.8 \times 10^{-6}$	0.674 mg/L in serum (mice) HED <sub>NOEL</sub> =0.000055 mg/kg-day	serum NOEL	30	Based on decreased plaque forming cell response in mice in a 60-day study. UF of 30: 10 for intraspecies differences and 3 for interspecies differences (Exhibit 3).

<sup>1</sup>The European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM) derived a tolerable weekly intake of 13 ng/kg-week for PFOS (equivalent to 1.8 ng/kg-day) based on increased total serum cholesterol in human epidemiological studies as part of a scientific opinion on the risks of PFOS in food. There is not a 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.

<sup>2</sup>Several agencies, including the Alaska Department of Environmental Conservation (2018), Connecticut State Department of Public Health (2016), Maine Center for Disease and Prevention (2017), Massachusetts Department of Environmental Protection (2018), Michigan Department of Environmental Quality (2018), and the Vermont Department of Health (2018) use the US EPA RfD and/or lifetime health advisory to define a health-based guidance value for PFOS in drinking water.

## EXHIBIT 1. PERFLUOROCTANE SULFONATE (PFOS)

### US EPA (2016a,b) REFERENCE DOSE DERIVATION AND LIFETIME DRINKING WATER HEALTH ADVISORY FOR PERFLUOROCTANE SULFONATE (PFOS).

**Source:** US EPA (United States Environmental Protection Agency). 2016b. Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). Office of Water. EPA 822-R-16-004. Last accessed (03/25/2019) at <https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-health-advisories-pfoa-and-pfos>.

## 5 DOSE-RESPONSE ASSESSMENT

As an initial step in the dose-response assessment, the NOAEL and/or LOAEL values were selected based on their NOAEL and/or LOAEL values. From these studies, the NOAEL values were selected (i.e., determination of HEDs) were selected. The pharmacokinetic model is limited because the NOAEL values for model input, as well as exposure to steady-state projections or applicable to the following short-term exposures. The pharmacokinetic model for the animal studies are restricted to the NOAEL values for PFOS intake.

As described in section 3.2.4, EPA used the NOAEL values to derive the average serum concentration from the toxicological database. Studies that demonstrated dose response and were available (AUC) at the time of sacrifice were used. The NOAEL values at the time of sacrifice with con-

The NOAEL, LOAEL, and effect i  
 average serum values and the percent  
 Table 5-1.

**Table 5-1. Human Equivalent**

<b>Study</b>	<b>Dosing duration days</b>	<b>NOAEL mg/kg/d</b>
Seacat et al. (2003): male rat ↑ALT, ↑BUN	98	0.34
Luebker et al. (2005b): ↓ rat pup body weight	84	0.1
Luebker et al. (2005a): ↓ rat pup body weight	63	None
Luebker et al. (2005a): rat ↓ maternal body weight, pup	63	0.4



## 5.1 Uncertainty Factors

An uncertainty factor for intraspecific variability in the responses within the life stage, health status) and extrinsic exposure. No information was available supports a factor other than 10.

An uncertainty factor for interspecific uncertainty in extrapolating from laboratory animals to humans. The three-fold factor is applied to account for pharmacokinetic differences between laboratory animals and humans. The HEDs were derived from the LOAELs of laboratory animals and humans. The HEDs were derived from the LOAELs of laboratory animals and humans.

An uncertainty factor for LOAEL to PODs, except the LOAEL of 0.4 mg/kg/day in the Luebker et al. (2005a) study. A value for the same effect was 0.1 mg/kg/day in the one-generation study. The value of 0.1 mg/kg/day was not used in the one-generation study. The value of 0.4 mg/kg/day, demonstrating that the

## 5.2 RfD Determination

Table 5-2 provides the calculation of the candidate RfD based on the NOAEL or LOAEL average serum PFOS values measures collected at the HED POD; Table 5-2 illustrates the HED PODs impacted by the doses used in the studies of the species/gender studied; therefore, the HED PODs, individual study characteristics, help to determine the RfD for humans. It is important to note the HED PODs and study durations evaluated.

**Table 5-2. Candidate RfDs Derived from HED PODs**

<b>POD</b>	<b>HED POD mg/kg/day</b>
(Seacat et al. 2003); male rat NOAEL for ↑ALT,	0.0013



from 0.00002 to 0.00005 mg/kg/day are calculated from HED average serum value is derived from reduced pup body weight derivation of the RfD for PFOS is the HED that represents approximately 30% of standard (3 UFA) was applied to the HED NOAEL supported by the 0.00002 mg/kg/day value from one-generation Luebker et al. (2005a) study on neurodevelopmental effects in the Buter

Low body weights in neonates are a problem that often manifests later in life. Pharmacokinetic modeling identified 0.4 mg/kg/day as the NOAEL for Wistar rat pups exposed during gestation to insulin resistance, problems with glucose tolerance as adults. A similar effect on glucose homeostasis was observed in a study by Wan et al. (2014) with a dose of 0.4 mg/kg/day of fat content. For animals receiving a high dose of PFOS, neurodevelopmental effects in Butenhol

indoor air in residential, commercial, paint, furniture, and other consumer products. PFOSA precursors that metabolically break down into PFOS. Sources include industrial use of PFOS, as well as its

PFOS has also been detected in soils, homes, offices, and vehicles. Incident to its use, PFOS can be transported by air route, particularly for small children. PFOS in soils and surface waters can affect crops, products, fish, and particulates in the

In summary, based on the physical and chemical properties of PFOS, there are many potentially significant exposure pathways. As outlined in its 2000 Methodology (USEPA 2000), there are many pathways of ingestion exist; however, information is limited on the relative contribution from all of these different sources (Birnbaum et al. 1998). The default RSC of 20% (0.20) for PFOS.

## **6.2 Lifetime Health Advisory**



The lifetime HA for PFOS is calculated as follows:  
A Drinking Water Equivalent Level (DWEL) is defined as the concentration of PFOS in drinking water that 100% of PFOS exposure comes from.

$$DWEL = \frac{RfD \times bw}{DWI/bw}$$

Where:

RfD = 0.00002 mg/kg/day; bw = 70 kg (adult body weight where dams were exposed through gestation and lactation);  
DWI/bw = 0.054 L/kg/day; 90 days (drinking water intake and indirect community water supply) (USEPA 2011b).

The lifetime HA is calculated as follows:



effects serving as the basis for the RfD  
(e.g., reduced ossification and accelera  
weight for PFOS; see USEPA 2016a, c

## EXHIBIT 2. PERFLUOROCTANE SULFONATE (PFOS)

MDH (2019) DERIVATION OF REFERENCE DOSE AND HEALTH-BASED WATER VALUE FOR  
PERFLUOROCTANE SULFONATE

**Source:** MDH (Minnesota Department of Health). 2019. Toxicological Summary for: Perfluorooctane Sulfonate. Last accessed (04/04/2019) at <https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf>.



## Toxicological Summary for

CAS: 45298-90-6 (anion)

1763-23-1 (acid)

29081-56-9 (ammonium salt)

70225-14-8 (diethanolamine salt)

2795-39-3 (potassium salt)

29457-72-5 (lithium salt)

Synonyms: PFOS, Perfluorooctane sulfo

***MDH conducted a focused re-evaluation***

Reference Dose/Concentration

Source of toxicity value

Point of Departure (POD)

Dose Adjustment Factor (DAF)

Human Equivalent Dose (HEC)

Total uncertainty factor (UF)

Uncertainty factor allocation

Toxicokinetic Model Description (Goer)

PFOS is well absorbed and is not metabolized. The model uses the following dose and clearance rate using the following:

*Serum Concentration*

*Where:*

*Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-d) × Concentration (mg/L)*  
*and*

*Clearance (L/kg-d) = Volume of distribution (L/kg) × Elimination Rate Constant (1/d)*

Two exposure scenarios were examined: 1) an infant exposed to contaminated water starting at birth and continuing through life; and 2) an infant exclusively breastfed from birth through life. In both scenarios the simulated serum concentration of PFOS (mg/L) was determined through placental transfer of PFOS (maternal to fetal) and breastmilk transfer of PFOS (maternal to infant).

Summary of Reasonable Maximum Exposure

Model Parameter	
Half-life	1241 d (5 <sup>th</sup> to 9 <sup>th</sup> )
Volume of distribution (Vd)	0.23 L/kg
Vd Age Adjustment Factor	2.1 age 10 years
Clearance Rate (CR)	0.0001 L/kg-d
Placental transfer factor <i>(% of maternal serum level)</i>	40% (n=10) the literature (Mean = 30%)
Breastmilk transfer factor <i>(% of maternal serum level)</i>	1.7% (n=10) reported (No 95 <sup>th</sup> percentile)
Water Intake Rate (L/kg-d)	95 <sup>th</sup> percentile 1 & 3-5 year olds
Breastmilk Intake Rate (L/kg-d)	Upper 95 <sup>th</sup> percentile



critical to note that background exposures are significantly lower than predicted while MDH's model predicts serum concentrations from a contaminated water source over time.

The apportionment to water ingestion was determined by subtracting a conservative (high-end) background exposure (0.8) from the total exposure (0.8). Eighty percent of the serum concentration is attributed to water (0.8). Subtracting the 95<sup>th</sup> percentile serum concentration (0.8) from the total exposure (0.8) as non-water background exposure leaves a residual serum concentration of 0.0. This residual concentration is attributed to water. This residual concentration is a residual serum concentration (RSC) of 24 µg/L and approximately 54% of the RSC of 50% for infants and young children.

Since exposures take years to eliminate, steady-state serum levels in older age groups are reached. Under steady-state conditions the 95<sup>th</sup> percentile (1.0) (Nelson 2018)) was used to determine the residual serum concentration under steady-state conditions.

Figure 1. Formula-fed infant scenario and an RSC of 50% for infants and you

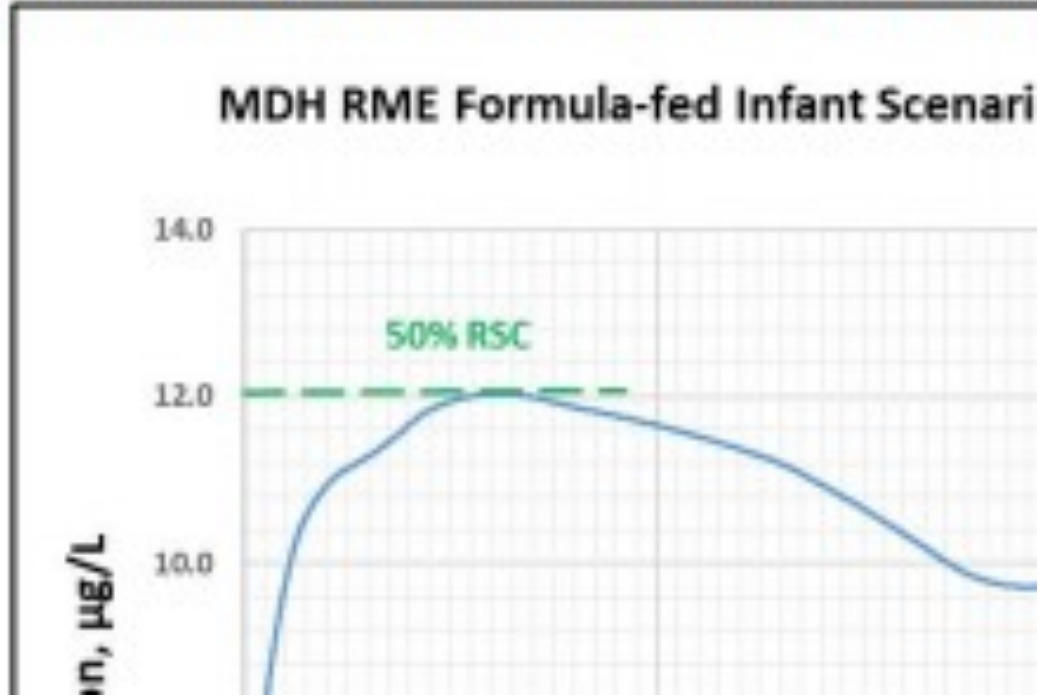


Figure 2. Formula-fed infant scenario se and an RSC of 20% for steady-state.

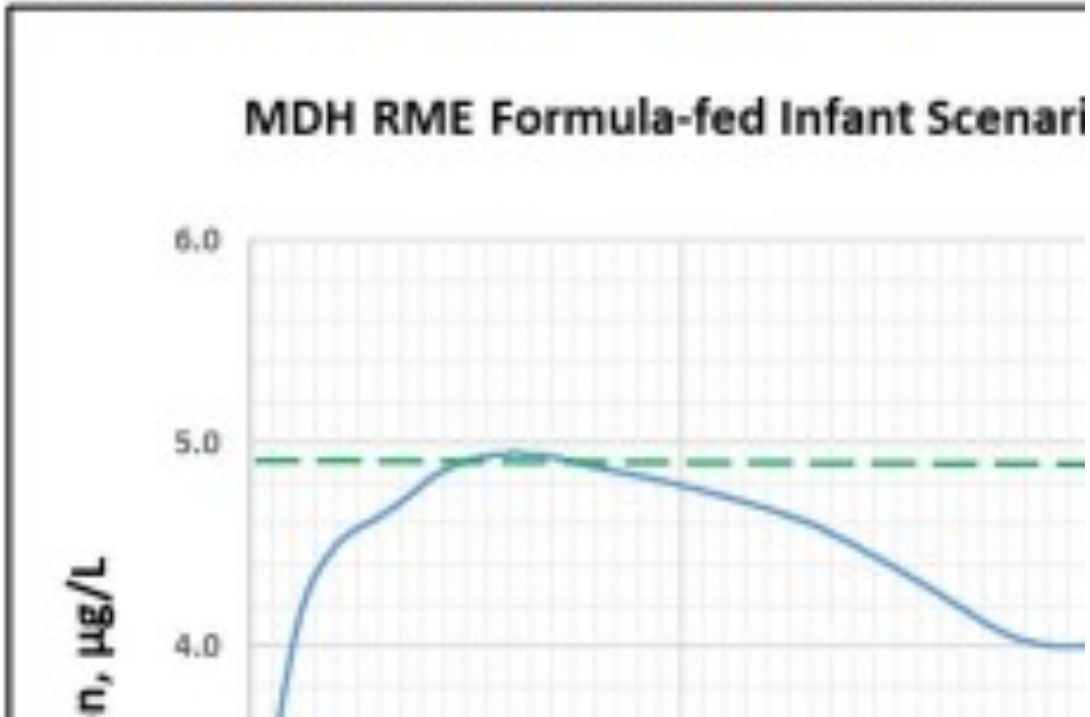
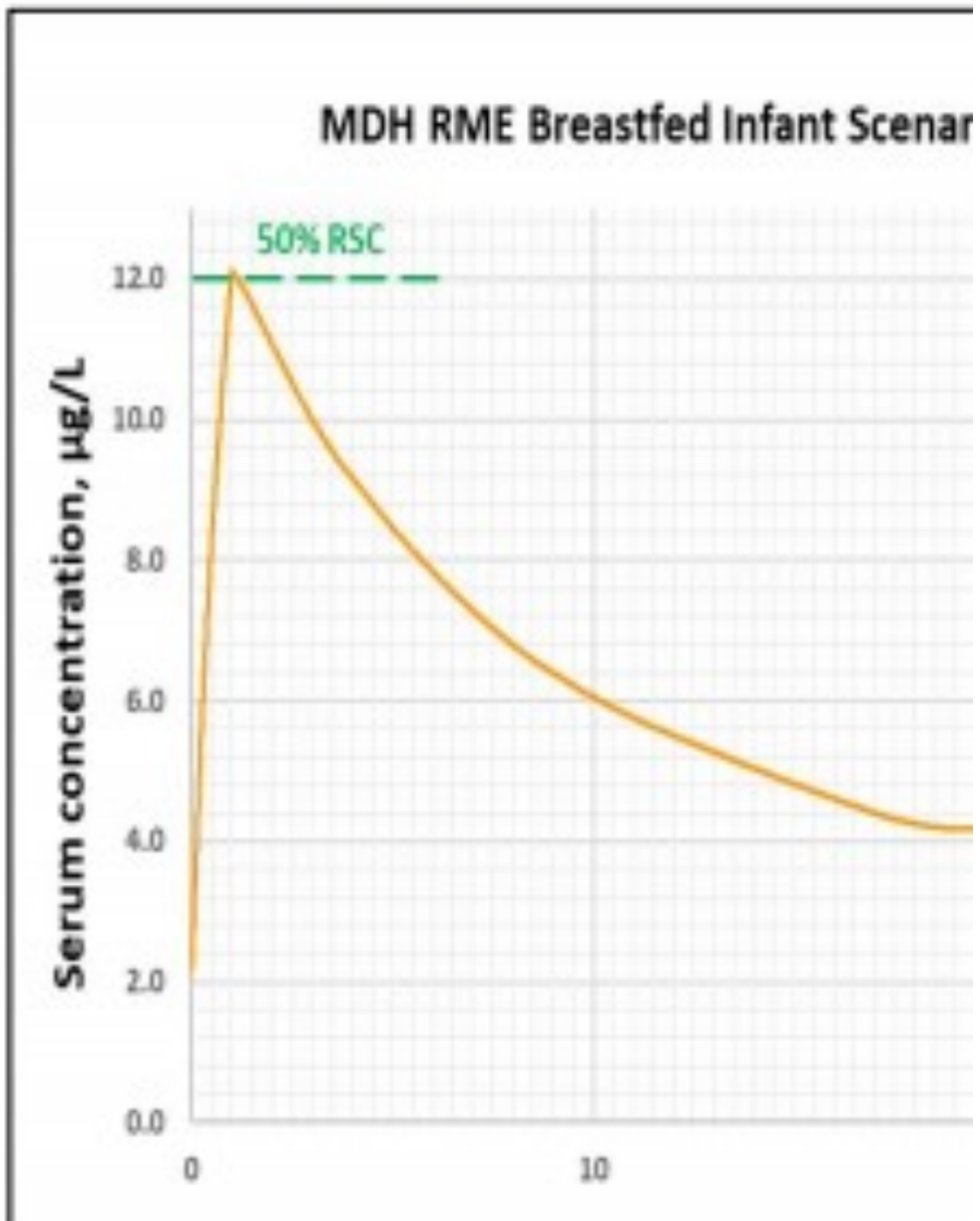




Figure 3. Breast-fed infant scenario scenario and an RSC of 50% for infants and you



## EXHIBIT 3. PERFLUOROOCCTANE SULFONATE (PFOS)

### NJ DWQI (2018) HEALTH-BASED MCL FOR PERFLUOROOCCTANE SULFONATE

Source: NJ DWQI (New Jersey Drinking Water Quality Institute). 2018. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). Health Effects Subcommittee. Last accessed (03/21/2019) at <https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf>.

## **DEVELOPMENT OF POTENTIAL HUMAN HEALTH ENDPOINTS**

The overall process used to develop potential human health endpoints is shown in Figure 15 and is discussed below. The MCLs for PFOS are based on serum PFOS levels rather than water levels. The MCLs are applied to the serum level PODs to develop Reference Doses (RfDs) but in terms of serum levels. Human Serum Levels are converted to Relative Source Contribution (RSC) administered doses to human serum levels. The RSC is the application of exposure factors for body weight, relative source contribution factor to account for the relative contribution of each source to the total exposure.

<b>Table 38. PODs, NOAELs and LOAELs and endpoints identified for dose-response relationships</b>	
<b><i>Study</i></b>	<b><i>Endpoint</i></b>
Butenhoff et al. (2012)	Hepatocellular hypertrophy (rats)
Dong et al. (2009)	Relative liver weight increase (male mice)
Dong et al. (2012a)	Relative liver weight increase (male mice)
Dong et al. (2009)	Decreased plasmacytoid cell forming immune response (male mice)

<sup>a</sup> Based on AUC

specific factors for which there is uncertainty of sensitive human sub-populations over factors of 1 (no adjustment), 3 or 10, with individual UFs represent log-units, the product UFs are considered in all cases:

**UF<sub>sub-chronic</sub>** – Applied to a sub-chronic NOAEL for a chronic duration study with an exposure of  $> 30$  day to  $\leq 90$  days.

**UF<sub>LOAEL</sub>** – Applied to an animal study without a corresponding NOAEL, when no NOAEL is available. The UF<sub>LOAEL</sub> has the value of 1 in all cases.



Decreased plaque forming cell response (mal

**UF<sub>sub-chronic</sub> = 1**

A sub-chronic to chronic unce  
sub-chronic POD to account f  
durations. The mice in Dong e  
a subchronic duration (i.e., >  
used because, as discussed in  
cell response based on serum  
to 60 days did not show a grea  
below). In summary, this ind

Table 40. Calculation of Target Human	
<i>Study</i>	<i>Animal</i> <i>(ng/ml)</i>
Butenhoff et al. (2012) (Hepatocellular hypertrophy)	4,5
Dong et al. (2012a) (Increased relative liver weight)	4,3
Dong et al. (2009) (Decreased plaque forming cell response)	6,

### Calculation of RfDs from Target Human S

The RfD (as an intake dose: mg/kg/day) is ca

### **Exposure factors for Health-based MCL**

The Health-based MCL is a PFOS drinking water consumption over a lifetime. The RfD for decreased plaque forming cell response (0.0001 mg/kg), daily drinking water ingestion (2 L/day; 20%; discussed below).

### **Relative Source Contribution (RSC) Factor**

A Relative Source Contribution (RSC) factor is used to estimate the contribution of each exposure pathway including food, soil, air, water, and consumer products to the total exposure. The RSC factor is used to estimate the contribution of each exposure pathway and other states in the development of health effects. The RSC factor is intended to be used for exposure estimates exceeding the RfD (USEPA, 2000b). Where drinking water exposure data is not available, the RSC factor is assumed to be 20% of exposure comes from drinking water. Where chemical-specific exposure data are available, the RSC factor is derived, with floor and ceiling RSC values.



than older individuals. Infants consume more than older individuals on a body weight basis and, PFOS concentrations in breast milk are similar or higher than in the mother's drinking water.

These higher infant exposures must be considered in the derivation of the MCL. A sensitive toxicological effect occurred from acute exposures in infancy. The dose-response for plaque forming cells in mice (an indicator of antibody response in humans) was similar for acute and chronic durations, indicating that the Reference Dose (RfD) is applicable to acute as well as chronic exposures.

For the reasons discussed above, the default MCL is based on the RfD.

### **Derivation of potential Health-based MCL**

The equation used to derive the Health-based MCL is:



## EXHIBIT 4. PERFLUOROOCCTANE SULFONATE (PFOS)

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

$1 \times 10^{-6}$	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 <sub>10</sub>	BMDL, 10% BMR
BMDL <sub>50</sub>	BMDL, 50% BMR
BMDL <sub>1SD</sub>	BMDL, BMR of one standard deviation
BMDL <sub>ADJ</sub>	BMDL, adjusted to continuous exposure
BMR	benchmark response
BW	body weight
BW <sup>2/3</sup>	body-weight raised to the 2/3 power scaling
BW <sup>3/4</sup>	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 <sub>1</sub>	first filial generation (in experimental animals)
F <sub>2</sub>	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 <sub>BMDL10</sub>	human equivalent dose at the BMDL <sub>10</sub>
HED <sub>LOEL</sub>	human equivalent dose at the LOEL
HED <sub>NOEL</sub>	human equivalent dose at the NOEL
HI	hazard index

#### EXHIBIT 4. PERFLUOROOCCTANE SULFONATE (PFOS)

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-day	liters per kilogram day
LADC	lifetime average daily concentration
LADD	lifetime average daily dose
LCL	lower confidence limit
LED	lower bound on effective dose
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
mcg	microgram
mcg/m <sup>3</sup>	micrograms per cubic meter
mcg/kg-day	micrograms per kilogram body weight per day
mcg/L	micrograms per liter
MCL	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 <sup>3</sup>	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 EPA
P (value)	probability value
PBPK	physiologically-based pharmacokinetic

#### EXHIBIT 4. PERFLUOROOCCTANE SULFONATE (PFOS)

PDAF	pharmacodynamic adjustment factor
pg	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