# APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

ATSDR uses the POD/uncertainty factor approach to derive MRLs. Potential PODs are NOAELs, LOAELs, or the BMDL. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals. ATSDR utilizes uncertainty factors to account for uncertainties associated with extrapolating from: (1) a LOAEL to a NOAEL; (2) extrapolating from animals to humans; and (3) to account for human variability (Chou et al. 1998; Pohl and Abadin 1995).

Default values of 10 are used for each of these categories of uncertainty factors; a value of 1 can be used if complete certainty exists for a particular uncertainty factor category. A partial uncertainty factor of 3 can be used when chemical-specific data decreases the uncertainty. On a case-by-case basis, ATSDR also utilizes modifying factors to account for MRL-specific database deficiencies.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

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# INTRODUCTION

## Overview of Epidemiological Studies

A large number of epidemiological studies have evaluated a wide range of potential health outcomes resulting from exposure to perfluoroalkyls, particularly PFOA and PFOS. The epidemiological studies fall into three broad categories: occupational exposure primarily to airborne PFOA and PFOS, exposure to PFOA-contaminated drinking water by residents living near a PFOA production facility, and general population exposure to background levels of perfluoroalkyls. Most of the occupational exposure studies were conducted in workers at four facilities in Minnesota, Alabama, West Virginia, and the Netherlands. Studies of the highly-exposed residents primarily come from several large-scale studies (C8 Health Project, C8 Health Study) of Mid-Ohio Valley residents living near the Washington Works facility in West Virginia who were exposed to high levels of PFOA in the drinking water. General population studies primarily utilized data collected in NHANES in the United States and several large-scale health studies conducted in Europe.

Most of the epidemiological studies lack environmental monitoring data and there is a potential for multiple sources of exposure (inhalation and oral). However, the majority of the epidemiological studies used serum perfluoroalkyl levels as a biomarker of exposure. One limitation of the C8 Health Studies is that they used blood samples collected in 2005–2006. However, the facility started using PFOA in the 1950s and peak usage was in the 1990s and by 2003, there was an 87% decline in PFOA emissions, as compared to 1999 levels (Emmett et al. 2006a). Therefore, serum PFOA levels measured in 2005–2006 likely do not represent earlier higher exposures, which may have contributed to observed health outcomes. As an alternative to using older serum PFOA levels, several C8 Health Studies estimated serum levels based on data on the release of PFOA from the facility and pharmacokinetic modeling. Of the three categories of subjects examined in the epidemiological studies, workers have the highest potential exposure to perfluoroalkyls, followed by the highly-exposed residents in the Mid-Ohio Valley (referred to as community exposure), and then the general population. In one study of workers at the Washington Works facility in West Virginia, the average serum PFOA level in 2001–2004 was 1,000 ng/mL (Sakr et al. 2007a); the mean PFOA level in community residents (without occupational exposure) near this facility was 423 ng/mL in 2004–2005 (Emmett et al. 2006a). By comparison, the geometric mean concentration of PFOA in the U.S. population was 3.92 ng/mL in 2005–2006 (CDC 2013).

**Identification of Adverse Health Effects Based on Epidemiological Studies.** Although a large number of epidemiological studies have examined the potential of perfluoroalkyls to induce adverse health effects, most of the studies were cross-sectional in design and do not establish causality. Epidemiological studies have found statistically significant associations between serum perfluoroalkyl levels and several health effects, although the results were not consistent across studies. Many of the studies reported dose-related trends, but these trends were not as apparent when comparing across studies; some effects were observed in populations with background PFOA levels but not in populations with high serum PFOA levels. Given the inconsistencies, ATSDR evaluated whether the preponderance of the data supported an association between perfluoroalkyl exposure and a particular health effect, taking into consideration the consistency of the findings across studies, the quality of the studies, dose-response, and plausibility. It should be noted that although the data may provide strong evidence for an association, it does not imply that the observed effect is biologically relevant because the magnitude of the change is within the normal limits or not indicative of an adverse health outcome. Plausibility depends primarily on experimental toxicology studies that establish a biological mechanism for the observed effects.

Using this approach, the available epidemiological data identify several potential health hazards of PFOA, PFOS, PFHxS, PFNA, and PFDA in humans as listed below.

***PFOA***

- Pregnancy-induced hypertension/pre-eclampsia
- Increases in serum hepatic enzymes, particularly alanine aminotransferase, and decreases in serum bilirubin levels
- Increases in serum lipids, particularly total cholesterol and LDL cholesterol
- Decreased antibody response to vaccines
- Small (<20 g or 0.7 ounces per 1 ng/mL increase in blood perfluoroalkyl level) decreases in birth weight

***PFOS***

- Pregnancy-induced hypertension/pre-eclampsia
- Liver damage, as evidenced by increases in serum enzymes and decreases in serum bilirubin levels
- Increases in serum lipids, particularly total cholesterol and LDL cholesterol
- Decreased antibody response to vaccines
- Small (<20 g or 0.7 ounces per 1 ng/mL increase in blood perfluoroalkyl level) decreases in birth weight

***PFHxS***

- Liver damage, as evidenced by increases in serum enzymes and decreases in serum bilirubin levels
- Decreased antibody response to vaccines

***PFNA***

- Increases in serum lipids, particularly total cholesterol and LDL cholesterol
- Decreased antibody response to vaccines (based on limited evidence)

***PFDA***

- Increases in serum lipids, particularly total cholesterol and LDL cholesterol
- Decreased antibody response to vaccines

**Limitations of Epidemiological Data.** There are sufficient epidemiological data to identify possible sensitive targets for many of the perfluoroalkyls; however, there are two major limitations to establishing dose-response relationships for these effects and using the epidemiological studies to derive MRLs: accurate identification of environmental exposure levels producing increased risk for adverse effects (exposure estimates and routes of exposure) and likely co-exposure to mixtures of perfluoroalkyls. Other limitations include the cross-sectional design of the majority of epidemiological studies and the potential that reverse causality contributes to the observed associations.

***Uncertainty in Exposure Estimates.*** In general, epidemiological studies provide a one-time serum perfluoroalkyl concentration, but lack information on actual environmental exposure concentration or doses, routes of exposure, and exposure duration. Although serum perfluoroalkyl levels provide reliable information on recent exposure (weeks to years, depending on the elimination $t_{1/2}$ for the perfluoroalkyl), they likely do not reflect historical exposure levels or exposure levels at the onset of the effect. This is especially true for occupational exposure cohorts where past exposure levels were higher before industrial hygiene improved and in the C8 community studies since peak PFOA levels in drinking water occurred at least 10 years prior to the onset of the studies. Additionally, data from NHANES suggest that some

perfluoroalkyl (PFOA, PFOS, PFHxS, and PFDA) levels are declining in the general population; for example, the geometric mean serum levels of PFOA and PFOS declined from 5.2 and 30.4 ng/mL, respectively, in 1999–2000 to 1.56 and 4.72 ng/mL in 2015–2016. In contrast, levels of PFNA have increased during that time frame; the geometric mean went from 0.5 ng/mL in 1999–2000 to 1.26 ng/mL in 2009–2010 and then decreased to 0.675 ng/mL in 2015–2016. Most studies do not provide adequate information to determine whether perfluoroalkyl levels reflect a steady state and relatively constant exposure, since most designs only include a single measurement. An added uncertainty occurs in studies that used maternal serum levels as the biomarker of exposure for effects in children or for effects on fertility.

It is assumed that workers were primarily exposed via inhalation; however, oral exposure may have also contributed to the total perfluoroalkyl body burden, particularly since workers frequently lived in communities with elevated levels of PFOA in the drinking water. It has been determined that drinking water was the primary source of perfluoroalkyls in residents living near a PFOA facility (Emmett et al. 2006a); however, it is likely that airborne PFOA contributed to overall body burden. Drinking water is the likely primary route of exposure for the general population.

***Uncertainty due to Co-Exposure to Other Perfluoroalkyls.*** Based on NHANES data, the U.S. general population is exposed to a variety of perfluoroalkyls. A number of studies reported a high degree of correlation between different perfluoroalkyls; however, most studies did not control for exposure to other perfluoroalkyls. Given that many of the perfluoroalkyls have similar targets of toxicity and possible mechanisms of action, it is likely that several perfluoroalkyls contributed to the observed effects. The potential interactions between different perfluoroalkyls have not been fully elucidated.

In summary, the epidemiological databases for several perfluoroalkyls provide valuable information on hazard identification; however, uncertainties regarding doses associated with adverse effects and possible interactions between compounds preclude use of these data to derive MRLs.

### Overview of Laboratory Animal Studies

Laboratory animal studies are available for 11 perfluoroalkyls (no data were located for PFHpA); however, more than 70% of the studies examined PFOA and/or PFOS. The laboratory animal studies primarily involved oral exposure and examined a wide range of potential health outcomes. The primary health effects observed in laboratory animals were liver toxicity, developmental toxicity, and immune toxicity. Other effects typically observed at higher doses included weight loss, histological alterations in reproductive tissues, and histological alterations in the thyroid gland. The sensitive targets of toxicity identified in the laboratory animals are similar to those observed in epidemiological studies.

**Limitations of Laboratory Animal Studies for Derivation of MRLs.** Use of controlled animal studies eliminates the uncertainties regarding effective doses and co-exposure to other perfluoroalkyls. However, there are uncertainties associated with derivation of MRLs based on animal studies, in part, because of large interspecies differences in the toxicokinetics of perfluoroalkyls for which mechanisms are not completely understood. Available information on the toxicokinetics of perfluoroalkyls in humans, nonhuman primates, and various rodent species indicate that elimination rates (and very likely elimination mechanisms and hormonal regulation of these mechanisms) vary substantially across chemical species (i.e., carbon chain length) and animal species (i.e., slower in humans compared to nonhuman primates and rodents), and show pronounced sex differences within certain species (e.g., faster elimination in female rats). As a result, there is some uncertainty associated with extrapolation of external dose-response relationships from animals to humans. Several PBPK models of PFOA and PFOS have been reported that simulate the substantial differences in pharmacokinetics of these compounds between humans and nonhuman primates or between humans and rats. These include human models for PFOA and PFOS (see

Section 3.1.5). An additional uncertainty in the animal data is the relevance of effects associated with activation of PPARα. Many of the effects observed in rodents, particularly liver and developmental effects, involve the activation of PPARα; humans and nonhuman primates are less responsive to PPARα agonists than rats and mice. However, studies in PPARα-null mice suggest that PPARα-independent mechanisms also play a role in the liver, immunological, and developmental toxicity.

## MRL Approach

The following approach was used for derivation of MRLs:

- Identify sensitive endpoints from epidemiological studies
- Identify laboratory animal studies that have evaluated dose-response relationships for toxicity targets identified in epidemiological studies
- Estimate a POD using animal serum perfluoroalkyl levels for sensitive endpoints
- Calculate HEDs using the assumption that a serum concentration resulting in an effect in a laboratory animal would also result in an effect in humans. An empirical pharmacokinetic model was used to estimate a human dose associated with this serum concentration for PFOA and PFOS. Measured serum concentrations in laboratory animal studies were used to calculate the HEDs for PFHxS and PFNA.
- Apply appropriate uncertainty factors informed by comparison of the POD to serum perfluoroalkyl levels reported in epidemiological studies

**Rationale for Internal Dose Metric Used in Dosimetry Extrapolation.** The time-weighted average serum concentration ($C_{TWA}$) was selected as the internal dose metric for dose-response modeling and dosimetry extrapolation. The $C_{TWA}$ was used rather than the maximum concentration ($C_{max}$) for the following reasons:

- $C_{TWA}$ provides a better representation of the history of exposure in the principal studies selected for the MRLs for PFOA (Koskela et al. 2016) and PFOS (Luebker et al. 2005a). The relatively slow elimination of PFOA and PFOS predicted in mice and rats results in a build-up of serum concentrations during the exposure duration. As a result, the $C_{max}$ is predicted to occur soon after the last dose in these studies (based on the Wambaugh et al. 2013 model).

- The assumption that must be accepted to justify using the $C_{max}$ is that only the last dose of PFOA or PFOS, which results in the $C_{max}$, determines the toxicity outcome, and the earlier exposure history contributes only by building up the levels to the $C_{max}$.

- The available data on the toxicity of PFOA and PFOS do not provide convincing evidence that toxicity outcomes are more likely to be determined by $C_{max}$ rather than the exposure history, represented by $C_{TWA}$.

- Given that $C_{max}$ is predicted to exceed $C_{TWA}$ in the principal studies (based on the Wambaugh et al. 2013 model), the resulting HED that achieves a steady-state serum concentration equal to the $C_{max}$ would be larger than the corresponding HED based on $C_{TWA}$. In the absence of strong evidence for $C_{max}$ being a more appropriate dose metric than $C_{TWA}$, use of $C_{TWA}$ for dosimetry extrapolation is an appropriate health-protective assumption in the derivation of the MRL.

**Predicting Mean Serum PFOA and PFOS Concentrations in Laboratory Animals.** TWA serum concentrations corresponding to external doses (mg/kg/day) and exposure durations (days) were predicted with a pharmacokinetic (PK) model for the animal species, strain, and sex used in the studies (Wambaugh et al. 2013). The Wambaugh et al. (2013) model was selected over other available

pharmacokinetic models for the following reasons: (1) it provided a single model structure (parameters) for simulating kinetics of PFOA and PFOS; (2) Wambaugh et al. (2013) derived parameter values for sex-specific species and strains used in the candidate principal studies for the oral MRLs (female and male CD1 mouse, C57BL/6 mouse, Sprague-Dawley rat, cynomolgus monkey); and (3) models were calibrated using Bayesian parameter estimation based on multiple PFOA (n=6) and PFOS (n=2) pharmacokinetics studies for specific species, strains, and sexes; and were then evaluated by comparing predicted and observed serum concentrations from toxicology studies performed on the same species, strains, and sex. Predicted and observed terminal serum concentrations for PFOA and PFOS agreed within a factor of 2, showed strong linear correlation, and distributed symmetrically along the line of identity, suggesting minimal bias in predictions across species, strains, and sexes.

The TWA serum concentration was calculated as follows (Equation A-1):

$$C_{TWA} = \frac{C_{AUC}}{ED} \qquad \text{Eq. (A-1)}$$

where $C_{TWA}$ is the predicted TWA serum concentration (mg/L), $C_{AUC}$ is the predicted area under the curve (AUC) of the serum concentration-time profile for the exposure (mg hour/L), and *ED* is the exposure duration (hour). Gavage studies were simulated as a single dose (e.g., gavage) given once every 24 hours. Daily drinking water exposures were simulated as a 12-hour period of dosing followed by 12 hours with no dosing. This assumes that the animals consumed water during a 12-hour active period and received the total daily dose during this 12-hour period. The dosing interval was 0.1 hour.

The Wambaugh et al. (2013) model was originally implemented in R (v2.10.0) and was migrated to MATLAB (vR2016) for calculations of MRLs. Wambaugh et al. (2013) reported mean and confidence limits for parameter values estimated from a Bayesian Markov Chain Monte Carlo (MCMC) analysis. The posterior means were used as point estimates for parameters in the MATLAB version. Function of the point estimate implementation in MATLAB was verified by comparing predictions of $C_{AUC}$ obtained from the MATLAB version with predictions from the MCMC analysis reported in EPA (2016e, 2016f). This comparison for PFOA included a total of 18 predictions of $C_{AUC}$ for female CD-1 mice (Lau et al. 2006; Wolf et al. 2007), female C57Bl6 mice (DeWitt et al. 2008), and male Sprague-Dawley rats (Butenhoff et al. 2004b). The $r^2$ for MATLAB vs R predictions of $C_{AUC}$ was 0.99 and the average relative percent difference (MATLAB-R) was 2.8% (range: -6.6–13.5). The comparison for PFOS included a total of 28 predictions of $C_{AUC}$ for female CD-1 mice (Lau et al. 2003), female Sprague-Dawley rats (Butenhoff et al. 2009b; Lau et al. 2003; Luebker et al. 2005a, 2005b), and male and female Cynomolgus monkeys (Seacat et al. 2002). The $r^2$ for MATLAB vs R predictions of $C_{AUC}$ was 1.00 and the average relative percent difference (MATLAB-R) was 4.6% (range: -11–20).

**Estimating TWA Serum PFHxS and PFNA Concentrations in Laboratory Animals.** Because a PK model for predicting the TWA serum concentrations was not identified for PFHxS and PFNA, a TWA serum concentration was estimated from measured serum concentrations. ATSDR estimated the TWA values from the areas under the curve calculated using the trapezoid rule. Since most studies did not report pre-exposure levels, serum concentrations in the control group were used as the baseline concentration.

**Estimating HEDs for Perfluoroalkyls.** The serum concentration PODs identified from the laboratory animal data were converted to an equivalent dose in humans, which is defined as the continuous ingestion dose (mg/kg/day) that would result in steady-state serum concentrations of perfluoroalkyl equal to the serum concentration (µg/mL) selected as the POD. Although human PBPK models for PFOA and PFOS have been reported, the simpler empirical model was selected for deriving

HEDs for the following reasons. Human PBPK models have not been validated with observations made in humans for which individual exposures were known with sufficient certainty to evaluate confidence in predicting dose-serum concentration relationships. Calibration and validation of human PBPK models have relied on comparing predicted and observed declines in serum concentrations following declines or cessation of exposure (Fàbrega et al. 2014, 2016; Loccisano et al. 2011; Worley et al. 2017b). This approach validates the ability of the models to predict serum concentration half-lives, which can be estimated directly from the observation data and represented in the empirical model. However, it does not validate the ability of the models to predict serum concentration in association with known exposures. Worley et al. (2017b) reported good agreement between the distribution of observed and predicted serum concentrations of PFOA within a study population, when assumptions about variability in exposure and biokinetics were incorporated into the simulations.

The relationship between perfluoroalkyl external dosage (mg/kg/day) and steady-state serum concentration ($C_{ss}$, mg/L) in humans was estimated assuming a single-compartment first-order model in which elimination kinetics are adequately represented by observed serum elimination $t_{1/2}$ values for the specific perfluoroalkyl, an assumed apparent volume of distribution ($V_d$, L/kg) and gastrointestinal absorption fraction. In the first-order single-compartment model, continuous exposure will result in a steady-state body burden ($BB_{SS}$, mg/kg) for PFOA or PFOS, which will be distributed in a single volume of distribution to yield a steady-state serum concentration (Equation A-2):

$$C_{SS} = \frac{BB_{SS}}{V_d} \quad \text{Eq. (A-2)}$$

At steady state, the rate of first-order elimination rate (a constant fraction of the body burden, $k_e$ per day) will equal the absorbed dosage ($D_{ss}$, mg/kg/day) adjusted for gastrointestinal absorption (AF) (Equation A-3):

$$D_{SS} \cdot AF = BB_{SS} \cdot k_e \quad \text{Eq. (A-3)}$$

Rearrangement of Equation A-3 allows calculation of the steady-state body burden corresponding to a given external dosage (Equation A-4):

$$BB_{SS} = \frac{D_{SS} \cdot AF}{k_e} \quad \text{Eq. (A-4)}$$

The relationship between the elimination rate constant ($k_e$, $day^{-1}$) and the elimination half-life ($t_{1/2}$, day), is given in Equation A-5:

$$k_e = \frac{\ln(2)}{t_{1/2}} \quad \text{Eq. (A-5)}$$

Combining Equations A-2 and A-3 yields an expression relating the external steady-state dosage and steady-state serum concentration (Equation A-6):

$$D_{SS} = \frac{C_{SS} \cdot k_e \cdot V_d}{AF} \quad \text{Eq. (A-6)}$$

The above estimates of $C_{SS}/D_{SS}$ are sensitive to the input parameters, $t_{1/2}$, AF, and $V_d$. The empirical model used to calculate HEDs is linear; therefore, the change in the HED is approximately proportional to the change in the half-life. A halving of the half-life would result in a doubling of the HED.

***PFOA and PFOS.*** Several studies have estimated PFOA and PFOS half-lives ($t_{1/2}$) in workers (Costa et al. 2009; Olsen et al. 2007a) or highly exposed residents (Bartell et al. 2010). Estimates of the half-lives based on Olsen et al. (2007a) were derived from longitudinal measurements of serum concentrations of PFOA and PFOS in a group of fluorochemical production workers (24 males, 2 females); the estimated half-lives were 3.8 years (95% confidence limit [CL] 3.1–4.4) and 5.4 years (95% CL 3.9–6.9), respectively. Costa et al. (2009) reported a half-life for PFOA of 5.1 years (SD 1.7) for a group of workers (n=16) following their cessation of PFOA production work. A longitudinal study by Bartell et al. (2010) followed serum PFOA concentrations in 200 subjects recruited from the Lubeck Public Service District and Little Hocking Water Association and followed for a period of 6–12 months after mitigation of exposures from drinking water. The estimated half-life for PFOA was 2.3 years (95% CL 2.1–2.4). A fourth study estimated half-lives in a cross-sectional study of residents served by the Lubeck Public Service District and Little Hocking Water Association (Seals et al. 2011). The estimated half-lives ranged from 2.9 to 10.1 years (1,059–3,687 days) for PFOA. Results from the longitudinal studies are shown in Table A-1. For the MRL calculations, the PFOA half-life estimated by Olsen et al. (2007a) was selected over the half-life estimated by Bartell et al. (2010) because the Olsen et al. (2007a) study had a longer follow-up time (>5 years compared to 6–12 months) and estimates of the terminal half-life appear to increase with longer follow-ups because slower kinetics make a larger contribution to the terminal half-life (Seals et al. 2011). This may reflect a larger contribution of slower kinetics or ongoing exposure to the terminal half-life observable with longer follow-ups (Worley et al. 2017a) or other factors such as differences in the age-distribution of the populations studied. The decision to use the longer half-life from Olsen et al. (2007a) is also health protective in that a longer half-life would result in higher predicted serum concentrations for a given intake and, therefore, lower HEDs for a given serum concentration POD. Estimates of the half-life for PFOA and PFOS are most applicable to serum concentrations within the above ranges and would be less certain if applied to serum concentrations substantially below or above these ranges. Serum concentrations during the 5-year observation period in the Olsen et al. (2007a) study are provided in Table A-2.

**Table A-1. Half-Life PFOA and PFOS Levels in Humans**

| PFOA $t_{1/2}$ (days) | PFOS $t_{1/2}$ (days) | Exposure type | Number | Source |
|---|---|---|---|---|
| 1,378 | 1,976 | Occupational | 26 | Olsen et al. (2007a) |
| 1,862 | NA | Occupational | 16 | Costa et al. (2009) |
| 840 | NA | Environmental | 200 | Bartell et al. (2010) |

NA = not available; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

**Table A-2. Serum PFOA and PFOS Concentrations Measured in Fluorochemical Production Workers**

| | PFOA (ppb) | PFOS (ppb) |
|---|---|---|
| Initial | 408 (72, 5,100) | 626 (145, 3,490) |
| Final | 148 (17, 2,435) | 295 (37, 1,740) |

PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: Olsen et al. 2007a

Estimates of volume of distribution ($V_d$) are based on non-compartmental modeling of serum concentration kinetics in monkeys and are assumed to be applicable to humans at the above serum concentrations (Table A-3).

**Table A-3. Apparent Volume of Distribution for PFOA and PFOS**

| PFOA $V_d$ (L/kg) | PFOS $V_d$ (L/kg) | Source |
|---|---|---|
| 0.18 (male)<br>0.20 (female) | NA<br>NA | Butenhoff et al. (2004c) |
| NA<br>NA | 0.20 (male)<br>0.27 (female) | Chang et al. (2012) |
| 0.3 | 0.3 | Harada et al. (2005a) |

NA = not applicable; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Numerous studies conducted in various animal models provide evidence for approximately complete absorption of oral doses of PFOA and PFOS (i.e., AF≈1, see Section 3.1.1).

***PFHxS.*** For PFHxS, the estimate of the elimination t½ was derived from longitudinal measurements of serum concentrations of PFHxS in a group of retired fluorochemical production workers (24 males and 2 females) observed for a 5-year period; the estimated half-life was 8.5 years (3,109 days) (Olsen et al. 2007a). The range of initial serum concentrations was 16–1,295 ng/mL (mean of 290 ng/mL), and the final concentrations ranged from 10 to 791 ng/mL (mean of 182 ng/mL). Estimates of the t½ for PFHxS are most applicable to serum concentrations within the above ranges and would be less certain if applied to serum concentrations substantially below or above these ranges.

Estimates of volume of distribution ($V_d$) are based on non-compartmental modeling of serum concentration kinetics in monkeys and are assumed to be applicable to humans at the above serum concentrations. Sundström et al. (2012) estimated the apparent Vd for PFHxS at 0.287 L/kg for male Cynomolgus monkeys and at 0.213 L/kg for female Cynomolgus monkeys.

Few studies have been conducted in animals that provide estimates for a gastrointestinal absorption factor of oral doses of PFHxS. Sundström et al. (2012), based on comparison of the AUC for oral and intravenous administration, estimated an oral absorption fraction for PFHxS (administered as a single 10 mg/kg dose) of 50% in female rats. However, as the authors point out, this estimate may not be reliable due to the short (24 hours) observation period (Sundström et al. 2012) and that "female $C_{max}$ values did not differ significantly between the oral and IV doses, and $T_{max}$ after oral dosing was estimated to be at approximately 30 min." These latter observations suggest approximately complete bioavailability. The AUC for male rats following oral exposure was not available, and the AUC after

intravenous administration was done in only one male rat (Sundström et al. 2012). A study conducted by Kim et al. (2016) in rats estimated an approximately 100% oral bioavailability based on the $C_{max}$ value and AUC comparison between oral and intravenous doses. Therefore, an absorption fraction (AF) of 1 was used for PFHxS.

***PFNA.*** For PFNA, the elimination half-life estimates were derived by paired blood and urine samples (n=86) from Chinese adults in a study that measured the concentrations of a number of perfluoroalkyls, including PFNA (Zhang et al. 2013). The participants were first divided into four groups; young females (age ≤50 years, n=20), older females (>50 years, n=19), young males (≤50 years, n=32), and older males (>50 years, n=15). The group of young females had significantly lower levels of perfluoroalkyls than the other groups; therefore, the three other groups were combined. The lower perfluoroalkyl levels were likely due to the elimination via menstrual bleeding, pregnancy, and lactation. The estimated arithmetic mean elimination half-lives for the young female group and the combined male and older female group for PFNA were 2.5 and 4.3 years (913 and 1,570 days), respectively.

Toxicokinetics parameters for perfluorocarboxylic acids, among them PFOA and PFNA analogs, were investigated in rats by Ohmori et al. (2003). The authors estimated that the $V_d$ values in steady state were not much different between the perfluorocarboxylic acids and between the sexes. Based on this, the estimated volume of distribution for PFNA in humans will be assumed to be the same for PFOA, 0.2 L/kg.

There are no studies on absorption of PFNA in humans. In rodents, oral absorption occurs rapidly as indicated by its presence in the serum of rodents soon after oral administration (Tatum-Gibbs et al. 2011). Therefore, based on animal studies of PFNA and other perfluorocarboxylic acid analogs, as well as sufficient findings of PFNA and other perfluorocarboxylic acids in human blood, it can be assumed that PFNA is well absorbed after oral exposure; therefore, an AF of 1 was used.

***Model Input Parameters.*** The first-order one-compartment model input parameters ($t_{1/2}$, $V_d$, and AF) are provided in Table A-4.

**Table A-4. First Order One-Compartment Model Parameters**

| Parameter | PFOA | PFOS | PFHxS | PFNA |
|---|---|---|---|---|
| Serum elimination half-life[a]; $t_{1/2}$ (day) | 1,400[a] | 2,000[a] | 3,100[a] | 900[b] |
| Serum elimination rate constant[c], $k_e$ ($day^{-1}$) | $4.95 \times 10^{-4}$ | $3.47 \times 10^{-4}$ | $2.23 \times 10^{-4}$ | $7.59 \times 10^{-4}$ |
| Gastrointestinal absorption fraction[d], AF | 1 | 1 | 1 | 1 |
| Apparent volume of distribution, $V_d$ (L/kg) | 0.2[e] | 0.2[e] | 0.287[f] | 0.2[e] |

[a]Estimates from Olsen et al. (2007a).
[b]Estimates from Zhang et al. (2013) for young females.
[c]Calculated using Equation 5.
[d]Based on studies in rodents and nonhuman primates.
[e]Estimates based on studies in nonhuman primates (Butenhoff et al. 2004c; Chang et al. 2012; Harada et al. 2005a).
[f]Estimates based on studies in nonhuman male primates (Sundström et al. 2012).

PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanoic acid (PFOA)
***CAS Numbers:*** 335-67-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFOA.

***Rationale for Not Deriving an MRL:*** Derivation of an inhalation MRL was precluded because inhalation-specific PBPK/pharmacokinetic model parameters are not available for PFOA and none of the studies reported serum PFOA concentrations.

Four studies have examined the acute toxicity of airborne PFOA in laboratory animals (Griffith and Long 1980; Kennedy et al. 1986; Staples et al. 1984). The observed effects included excessive salivation and eye and nose irritation in rats exposed to 18,600 mg/m$^3$ for 1 hour (Griffith and Long 1980), weight loss and pulmonary edema in rats exposed to 380 mg/m$^3$ for 4 hours (Kennedy et al. 1986), weight loss in rats exposed nose-only to 84 mg/m$^3$ 6 hours/day, 5 days/week for 2 weeks (Kennedy et al. 1986), and decreases in maternal weight gain at 10 mg/m$^3$ and maternal deaths and decreases in neonatal body weight at 25 mg/m$^3$ in rats exposed 6 hours/day on GDs 6–15 (Staples et al. 1984). The 2-week study also reported increases in liver weight and hepatocellular hypertrophy in rats exposed to 7.6 mg/m$^3$.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanoic acid (PFOA)
***CAS Numbers:*** 335-67-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFOA.

***Rationale for Not Deriving an MRL:*** No intermediate-duration inhalation studies in laboratory animals were identified for PFOA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanoic acid (PFOA)
***CAS Numbers:*** 335-67-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFOA.

***Rationale for Not Deriving an MRL:*** No chronic-duration inhalation studies in laboratory animals were identified for PFOA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanoic acid (PFOA)
***CAS Numbers:*** 335-67-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFOA.

***Rationale for Not Deriving an MRL:*** An acute-duration oral MRL cannot be derived for PFOA because the modeling approach used for estimating HEDs cannot be used to estimate acute human exposure where the exposure duration of 14 days is 1% of the elimination half-life in humans.

Acute-duration oral studies are available in rats and mice and provide information on body weight, hepatic, immunological, reproductive, and developmental effects. The liver effects consisted of increases in liver weight, hepatocellular hypertrophy, and/or decreases in serum cholesterol and triglycerides in rats and mice exposed to ≥1 mg/kg/day (Cook et al. 1992; Elcombe et al. 2010; Haughom and Spydevold 1992; Ikeda et al. 1985; Kawashima et al. 1995; Kennedy 1987; Liu et al. 1996; Pastoor et al. 1987; Iwai and Yamashita 2006; Permadi et al. 1992, 1993; Vetvicka and Vetvickova 2013; White et al. 2009; Wolf et al. 2007; Xie et al. 2003; Yang et al. 2000, 2001, 2002b). Consistent with the Hall et al. (2012) criteria (see Section 2.9 for a discussion of the criteria), the liver weight increases and hypertrophy observed in rats and mice were not considered relevant to human risk assessment. Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight and hepatocellular hypertrophy, and alterations in serum lipid levels observed in rats and mice, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs.

The immunological effects consisted of impaired responses to T-dependent antigens, such as sRBCs, altered antibody response, and decreases in spleen and thymus weights at 11.5 mg/kg/day and higher (DeWitt et al. 2009; Vetvicka and Vetvickova 2013; Yang et al. 2001, 2002a). Information on the potential reproductive toxicity of PFOA is limited to three studies that reported increases in serum estradiol levels in rats exposed to ≥2 mg/kg/day for 14 days (Biegel et al. 1995; Cook et al. 1992; Liu et al. 1996). A number of studies have evaluated the developmental toxicity of PFOA. In the only acute-duration developmental toxicity study in rats, no alterations in fetal body weight or malformations were observed at 100 mg/kg/day (Staples et al. 1984). Mice appear to be more sensitive to PFOA's developmental toxicity; observed effects include decreases in litter weight (Hu et al. 2010), decreases in pup body weight (White et al. 2007, 2009; Wolf et al. 2007), alterations in spontaneous activity (Johansson et al. 2008), increases in resorbed embryos (Chen et al. 2017b), and delays in mammary gland development (White et al. 2007, 2009; Wolf et al. 2007). The lowest LOAEL for developmental effects in mice was 0.5 mg/kg/day for decreased litter weight. A list of the NOAEL and LOAEL values for the immunological, reproductive, and developmental effects is presented in Table A-5.

**Table A-5. Summary of the Adverse Effects Observed in Laboratory Animals Following Acute-Duration Oral Exposure**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| ***Immunological*** | | | | |
| Mouse 10 days | | 11.5 | Decreased spleen and thymus weights | Yang et al. 2001 |
| Mouse 10 days | 7.5 | 15 | Altered response to sRBC | DeWitt et al. 2009 |
| Mouse 7 days | | 20 | Altered response to sRBC, decreased antibody formation | Vetvicka and Vetvickova 2013 |
| Mouse 7 days | | 24 | Decreased response to horse red blood cells | Yang et al. 2002a |
| ***Reproductive*** | | | | |
| Rat 14 days | 0.2 | 2 | 2-Fold increase in serum estradiol levels | Liu et al. 1996 |
| Mouse GDs 1–7 | | 2.5 | Decrease in the number of corpora lutea | Chen et al. 2017b |
| Rat 14 days | 1 | 10 | 63% increase in serum estradiol levels | Cook et al. 1992 |
| Rat 14 days | | 25 | 184% increase in serum estradiol levels | Biegel et al. 1995 |
| ***Developmental*** | | | | |
| Mouse GDs 6–17 | | 0.5 | Decreased litter weight on PND 2 | Hu et al. 2010 |
| Mouse PND 10 | | 0.58 | Decreased spontaneous behavior and altered response to cholinergic stimulant | Johansson et al. 2008 |
| Mouse GDs 8–17 or 12–17 | | 5 | Altered mammary gland development, decreased pup body weight on PND 20 | White et al. 2007 |
| Mouse GDs 8–17 | | 5 | Delayed mammary gland development, decreased pup body weight on PND 20 | White et al. 2007 |
| Mouse Various GDs | | 5 | Delayed mammary gland development; decreased pup body weight at weaning | White et al. 2009 Wolf et al. 2007 |

[a]LOAELs are for less serious effects.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; sRBC = sheep red blood cell

The lowest LOAEL values were identified for developmental effects; Hu et al. (2010) identified a LOAEL of 0.5 mg/kg/day for decreases in litter weight on PND 2 and Johansson et al. (2008) identified a LOAEL of 0.58 mg/kg for decreases in spontaneous behavior (locomotion and total activity) and decreased response to a cholinergic stimulant in adult mice exposed to PFOA on PND 10. Neither study identified NOAEL values.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanoic acid (PFOA)
***CAS Numbers:*** 335-67-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate
***MRL***: $3x10^{-6}$ mg/kg/day
***Critical Effect:*** Skeletal alterations in adult offspring
***Reference:*** Koskela et al. 2016
***Point of Departure:*** 0.000821 mg/kg/day
***Uncertainty Factor:*** 300
***LSE Graph Key:*** 63
***Species:*** Mouse

***MRL Summary:*** An intermediate-duration oral MRL of $3x10^{-6}$ mg/kg/day was derived for PFOA based on skeletal alterations at 13 and 17 months of age in the offspring of mice fed a diet containing PFOA on GD 1 through GD 21 (Koskela et al. 2016). The MRL is based on a HED LOAEL of 0.000821 mg/kg/day and a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

***Selection of the Critical Effect:*** Intermediate-duration oral studies of PFOA in animals indicate that the liver, immune system, reproductive system, and the developing organism are the primary targets of toxicity because adverse outcomes were observed at lower doses than other effects and have been consistently observed across studies. A summary of the lower LOAEL values (and associated NOAEL values) for these tissues/systems is presented in Table A-6; given the large number of studies, this table is limited to studies that identified LOAEL values of ≤4 mg/kg/day. Although these studies identified the lowest LOAEL values, not all were considered suitable as the basis of an intermediate-duration oral MRL.

Exposure to low levels of PFOA results in increases in liver weight, hepatocellular hypertrophy, and decreases in serum lipids in rats, mice, and monkeys exposed to PFOA for intermediate durations. The increases in liver weight, hepatocellular hypertrophy, and alterations in serum lipid levels observed in the rodents are likely adaptive responses to peroxisome proliferation and are not considered relevant for human risk assessment (Hall et al. 2012). Consistent with the Hall et al. (2012) criteria, the increases in liver weight and hepatocellular hypertrophy, in the absence of other degenerative alterations, were not considered adverse. Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight, hepatocellular hypertrophy, and alterations in serum lipid levels, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs.

A small number of animal studies have reported degenerative lesions, lesions to specialty cells, bile duct lesions, or inflammation; these endpoints were considered relevant for human risk assessment (Butenhoff et al. 2004b; Cui et al. 2009; Loveless et al. 2008). The lowest LOAEL for adverse liver effects was 0.96 mg/kg/day for increased liver weight, hepatocellular hypertrophy, and focal necrosis in mice exposed for 28 days (Loveless et al. 2008). *In utero* exposure has also resulted in liver effects in offspring (Filgo et al. 2015a; Quist et al. 2015a); the lowest maternal LOAEL identified in these studies was

0.01 mg/kg/day (Quist et al. 2015a). Because the Quist et al. (2015a) study did not provide incidence data for the reported inflammation, this study was not considered suitable for derivation of an MRL. Hepatic effects consisting of increases in absolute liver weight at ≥3 mg/kg/day and increases in serum triglyceride levels at 30/20 mg/kg/day have also been observed in monkeys administered capsules containing PFOA (Butenhoff et al. 2002); no histological alterations were observed in surviving animals, but hepatocellular degeneration and necrosis was noted in a monkey sacrificed early due to morbidity. The small number of animals examined and early deaths at several dose levels precludes using this study as the basis of an MRL.

Two studies examining the immunotoxicity of PFOA following intermediate-duration oral exposure found decreases in antigen-specific antibody responses in mice exposed for 15 days (DeWitt et al. 2008, 2016); the lowest LOAEL was 1.88 mg/kg/day (DeWitt et al. 2016). Reproductive and developmental toxicity studies have identified very low LOAELs of ≥0.0024 mg/kg/day for delays in mammary gland development in dams and offspring (Macon et al. 2011; Tucker et al. 2015; White et al. 2011). However, the mammary gland effect did not result in an adverse effect on lactational support at maternal doses as high as 1 mg/kg/day, based on normal growth and survival in F2 pups (White et al. 2011). Given that milk production was adequate to support growth, the biological significance of the delayed development of the mammary gland observed at very low doses is uncertain and was not considered a suitable basis for the MRL. Other developmental effects include increases in locomotor activity (Cheng et al. 2013; Goulding et al. 2017; Onishchenko et al. 2011; Sobolewski et al. 2014) at ≥0.1 mg/kg/day, reduced ossification of proximal phalanges and early preputial separation and delayed vaginal opening at ≥1 mg/kg/day (Lau et al. 2006; Yang et al. 2009), altered long bone morphology and decreased bone mineral density in 13- and 17-month-old mice following *in utero* exposure to 0.3 mg/kg/day (Koskela et al. 2016), decreases in pup survival at ≥0.6 mg/kg/day (Abbott et al. 2007; Albrecht et al. 2013), decreases in the number of successful births at ≥3 mg/kg/day (Ngo et al. 2014), and reduced neonatal weight gain and delayed eye opening at ≥3 mg/kg/day (Wolf et al. 2007).

**Table A-6. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| ***Hepatic*** | | | | |
| Mouse<br>GDs 1–17 | | 0.01 | Hepatocellular hypertrophy and periportal inflammation in offspring | Quist et al. 2015a, 2015b |
| Mouse<br>28 days | 0.29 | 0.96 | Moderate to severe hepatocellular hypertrophy and focal necrosis | Loveless et al. 2008 |
| Mouse<br>GDs 1–17<br>(examined at 18 months of age) | 0.3 | 1 | Increased severity of chronic inflammation in liver | Filgo et al. 2015a, 2015b |
| Rat<br>70–90 days | 1 | 3 | Increased liver weight, hepatocellular hypertrophy and necrosis | Butenhoff et al. 2004b |
| Monkey<br>26 weeks | | 3 | Increased absolute liver weight | Butenhoff et al. 2002 |

**Table A-6. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| ***Immunological*** | | | | |
| Mouse 15 days | 0.94 | 1.88 | Reduced antibody response | DeWitt et al. 2016 |
| Mouse 15 days | 1.88 | 3.75 | Reduced sRBC response | DeWitt et al. 2008 |
| ***Reproductive*** | | | | |
| Mouse GDs 1–17 | | 0.0024 | Delayed mammary gland development in dams (3-generation study) | White et al. 2011 |
| Mouse GDs 1–17 | | 1 | Delayed mammary gland development in dams (single-generation study) | White et al. 2011 |
| ***Developmental*** | | | | |
| Mouse GD 7–PND 22 | | 0.0024 | Impaired development of mammary glands | White et al. 2011 |
| Mouse GDs 10–17 | | 0.01 | Impaired development of mammary glands | Macon et al. 2011 |
| Mouse GDs 1–17 | | 0.01 | Impaired development of mammary glands | Tucker et al. 2015 |
| Mouse GD 7–PND 21 | | 0.1 | Neurodevelopmental | Sobolewski et al. 2014 |
| Mouse GDs 1–21 | | 0.3 | Altered exploratory behavior in adult offspring; increased global activity in males | Onishchenko et al. 2011 |
| Mouse GDs 1–21 | | 0.3 | Skeletal alterations in mature offspring | Koskela et al. 2016 |
| Mouse GDs 1–17 | | 0.3 | Impaired development of mammary glands | Macon et al. 2011 |
| Mouse GDs 1–17 | 0.3 | 0.6 (SLOAEL) | Decreased pup survival | Abbott et al. 2007 |
| Mouse GDs 1–17 | | 1 | Reduced ossification of proximal phalanges and advanced preputial separation | Lau et al. 2006 |
| Mouse 4 weeks starting at PND 21 | | 1 | Delayed vaginal opening | Yang et al. 2009 |
| Mouse GDs 1–17 | 0.3 | 1 | Increased ambulatory activity | Goulding et al. 2017 |
| Rat GD 1–PND 21 | | 1.6 | Neurodevelopmental | Cheng et al. 2013 |
| Mouse GDs 1–17 | 0.1 | 3 | Decreased number of successful births | Ngo et al. 2014 |

**Table A-6. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| Mouse GDs 1–17 | | 3 | Reduced pups per litter on PND 20 | Albrecht et al. 2013 |
| Mouse GDs 1–17 | | 3 | Reduced weight gain, delayed eye opening | Wolf et al. 2007 |

[a]Unless otherwise noted, LOAELs are for less serious effects.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; SLOAEL = serious LOAEL; sRBC = sheep red blood cell

***Selection of the Principal Study:*** As outlined in the MRL approach section, serum PFOA levels were predicted for the administered doses for most of the studies listed in Table A-6. Mean serum PFOA levels could not be predicted for four studies because pharmacokinetic model parameters were not available for Wistar rats (Cheng et al. 2013), male CD-1 mice (Loveless et al. 2008), or 129S1/SvlmJ wild-type mice (Abbott et al. 2007; Albrecht et al. 2013). A summary of the predicted serum PFOA levels is presented in Table A-7.

**Table A-7. Summary of the Predicted TWA Serum PFOA levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Predicted TWA serum PFOA (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| ***Hepatic*** | | | | |
| CD Mouse 28 days | 0.29<br>0.96<br>9.6 | Not calculated | Moderate to severe hepatocellular hypertrophy and focal necrosis at 0.96 mg/kg/day | Loveless et al. 2008 |
| 129/Sv Mouse GDs 1–17 | 0.01<br>0.1<br>0.3<br>1<br>5 | 0.423<br>4.21<br>12.5<br>39.2<br>102 | Increased severity of chronic inflammation in liver of offspring aged 18 months at 1 mg/kg/day | Filgo et al. 2015a, 2015b |
| Sprague-Dawley Rat 70–90 days | 1<br>3<br>10<br>30 | 60.4<br>136<br>222<br>242 | Increased liver weight, hepatocellular hypertrophy and necrosis at 10 mg/kg/day | Butenhoff et al. 2004b |
| Cynomolgus Monkey 6 months | 3<br>10<br>20/30 | 68.5<br>93.8<br>113 | Increased liver weight at 3 mg/kg/day | Butenhoff et al. 2002 |

**Table A-7. Summary of the Predicted TWA Serum PFOA levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Predicted TWA serum PFOA (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| ***Immunological*** | | | | |
| C58BL/6N Mouse 15 days | 0.94 | 21.4 | Reduced antibody response at 1.88 mg/kg/day | DeWitt et al. 2016 |
| | 1.88 | 42.5 | | |
| | 3.75 | 58.4 | | |
| | 7.5 | 83.5 | | |
| C57BL/6N Mouse 15 days | 0.94 | 21.4 | Reduced sRBC response at 3.75 mg/kg/day | DeWitt et al. 2008 |
| | 1.88 | 42.5 | | |
| | 3.75 | 58.4 | | |
| | 7.5 | 83.5 | | |
| | 15 | 109 | | |
| | 30 | 149 | | |
| ***Developmental*** | | | | |
| C57BL/6 Mouse GD 7–PND 21 | 0.1 | 2.23 | Neurodevelopmental effects (increased horizontal and vertical activity and decreased resting activity) at 0.1 mg/kg/day | Sobolewski et al. 2014 |
| C57BL/6 Mouse GDs 1–21 | 0.3 | 8.29 | Skeletal alterations at 0.3 mg/kg/day | Koskela et al. 2016 |
| C57BL/6 Mouse GDs 1–21 | 0.3 | 8.29 | Neurodevelopmental (decreased number of inactive periods, altered novelty induced activity) at 0.3 mg/kg/day | Onishchenko et al. 2011 |
| 129S1/SvlmJ Mouse GDs 1–17 | 0.1 | Not calculated[a] | Decreased pup survival at 0.6 mg/kg/day | Abbott et al. 2007 |
| | 0.3 | | | |
| | 0.6 | | | |
| | 1 | | | |
| | 3 | | | |
| | 5 | | | |
| | 10 | | | |
| | 20 | | | |
| CD-1 Mouse GDs 1–17 | 1 | 39.2 | Reduced ossification of proximal phalanges and advanced preputial separation at 1 mg/kg/day | Lau et al. 2006 |
| | 3 | 83.6 | | |
| | 5 | 102 | | |
| | 10 | 125 | | |
| | 20 | 155 | | |
| | 40 | 205 | | |

**Table A-7. Summary of the Predicted TWA Serum PFOA levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Predicted TWA serum PFOA (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| Mouse 4 weeks starting at PND 21 | 1<br>5<br>10 | Not calculated | Delayed vaginal opening | Yang et al. 2009 |
| Mouse GDs 1–17 | 0.1<br>0.3<br>1 | 4.21<br>12.5<br>39.2 | Increased ambulatory activity at 1 mg/kg/day | Goulding et al. 2017 |
| Wistar Rat GD 1–PND 21 | 1.6 | Not calculated | Neurodevelopmental effects (increased locomotor activity in males and decreased activity in females) at 1.6 mg/kg/day | Cheng et al. 2013 |
| C57BL/6J Mouse GDs 1–17 | 0.1<br>3 | 2.43<br>62.0 | Decreased number of successful births at 3 mg/kg/day | Ngo et al. 2014 |
| SV/129 Mouse GDs 1–17 | 3 | Not calculated[b] | Reduced pups per litter on PND 20 at 3 mg/kg/day | Albrecht et al. 2013 |
| CD-1 Mouse GDs 1–17 | 3<br>5 | 84.8<br>102 | Reduced weight gain, delayed eye opening at 3 mg/kg/day | Wolf et al. 2007 |

[a]Reported serum PFOA concentrations at weaning for the dams that did not have pups which survived to weaning were 4.4, 10.4, 17.4, 26.3, 76.6, 72.4, and 68.2 µg/mL in the 0.1, 0.3, 0.5, 1, 5, 10, and 20 mg/kg/day group, respectively.
[b]Reported serum PFOA concentration was 17 µg/mL for dams treated with 1.6 mg/kg/day.

GD = gestation day; PFOA = perfluorooctanoic acid; PND = postnatal day; sRBC = sheep red blood cell; TWA = time-weighted average

***Selection of the Point of Departure for the MRL:*** The NOAEL/LOAEL and the benchmark dose (BMD) approaches were utilized to identify potential PODs for derivation of the intermediate-duration oral MRL for PFOA. The only datasets with predicted TWA serum PFOA levels amenable to BMD modeling were from the DeWitt et al. (2008, 2016) immunotoxicity studies and Lau et al. (2006) developmental toxicity study. The Sobolewski et al. (2014), Onishchenko et al. (2011), Koskela et al. (2016), Ngo et al. (2014), and Wolf et al. (2007) studies were not considered for BMD modeling because only one or two PFOA doses were tested. No adequate BMD models adequately fit the data from the Lau et al. (2006) study. Adequate fit was found for the DeWitt et al. (2008, 2016) studies; the BMD modeling results are presented at the end of this section.

HEDs were calculated for each potential PODs (NOAEL, LOAEL, or BMD value) identified in laboratory animal studies using the first order single-compartment model previously discussed and the assumption that humans would have similar effects as the laboratory animal at a given serum concentration. The HEDs for each POD are presented in Table A-8. The potential $POD_{HED}$ values were divided by an uncertainty factor to calculate candidate MRLs; these values are also presented in Table A-8. The candidate MRLs range from $7.4x10^{-7}$ mg/kg/day for neurodevelopmental effects in mice

(Sobolewski et al. 2014) to $4.5x10^{-4}$ mg/kg/day for liver effects in male rats (Butenhoff et al. 2004b). The lowest LOAEL (expressed as predicted serum concentration) was identified in the Sobolewski et al. (2014) study, which found neurodevelopmental effects in mouse offspring at predicted serum PFOA concentration of 2.23 µg/mL. However, this study was not considered suitable as the basis of the MRL because the subroute and vehicle used for the controls (peanut oil with anisole administered via gavage) were different from the PFOA group (PFOA dissolved in water and added to diet). Rather, the Onishchenko et al. (2011) and Koskela et al. (2016) studies, which identified the second lowest LOAEL (serum PFOA concentration) of 8.29 µg/mL were considered. In the Onishchenko et al. (2011) study, circadian activity was assessed using a TrafficCage in which all animals in the group were placed in a single cage and activity was measured. Thus, activity was only measured on a group basis and it is possible that one animal could skew the results. Thus, this study was not considered a suitable basis for an MRL.

**Table A-8. Summary of Potential Points of Departures (PODs) and Human Equivalent Doses (HEDs) for Intermediate-Duration Oral MRL for PFOA**

| | Predicted serum concentrations (µg/mL) | | | | |
|---|---|---|---|---|---|
| Endpoint (reference) | NOAEL or BMDL | LOAEL | $POD_{HED}$[a] (mg/kg/day) | Total UF | Candidate MRLs (mg/kg/day) |
| Neurodevelopmental effects (increased horizontal and vertical activity and decreased resting activity) in mice (Sobolewski et al. 2014) | | 2.23 | 0.000221 | 300[b] | $7.4x10^{-7}$ |
| Neurodevelopmental effects (decreased number of inactive periods, altered novelty induced activity) in mice (Onishchenko et al. 2011) | | 8.29 | 0.000821 | 300[b] | $2.7x10^{-6}$ |
| Skeletal alterations in mice (Koskela et al. 2016) | | 8.29 | 0.000821 | 300[b] | $2.7x10^{-6}$ |
| Decreased number of successful births in mice (Ngo et al. 2014) | 2.43 | 62.0 | 0.000241 | 30[c] | $8.0x10^{-6}$ |
| Reduced ossification of proximal phalanges and advanced preputial separation in mice (Lau et al. 2006) | | 39.2 | 0.00388 | 300[b] | $1.3x10^{-5}$ |
| Increased ambulatory activity (Goulding et al. 2017) | 12.5 | 39.2 | 0.00124 | 30[c] | $4.1x10^{-5}$ |
| Reduced weight gain and delayed eye opening (Wolf et al. 2007) | | 84.8 | 0.00840 | 300[b] | $2.8x10^{-5}$ |
| Reduced response to dinitrophenyl-ficoll (DNP) antigen in female mice (DeWitt et al. 2016) | 12.23 ($BMDL_{1SD}$) | | 0.00121 | 30[c] | $4.0x10^{-5}$ |
| Increased severity of chronic inflammation in liver of offspring aged 18 months (Filgo et al. 2015a, 2015b) | 12.5 | 39.2 | 0.00124 | 30[c] | $4.1x10^{-5}$ |

**Table A-8. Summary of Potential Points of Departures (PODs) and Human Equivalent Doses (HEDs) for Intermediate-Duration Oral MRL for PFOA**

| Endpoint (reference) | Predicted serum concentrations (µg/mL) NOAEL or BMDL | LOAEL | $POD_{HED}$[a] (mg/kg/day) | Total UF | Candidate MRLs (mg/kg/day) |
|---|---|---|---|---|---|
| Reduced response to sRBC in female mice (DeWitt et al. 2008) | 33.49 ($BMDL_{1SD}$) | | 0.00332 | 30[c] | $1.1x10^{-4}$ |
| Increased liver weight, hepatocellular hypertrophy, and necrosis in male rats (Butenhoff et al. 2004b) | 136 | 222 | 0.0135 | 30[c] | $4.5x10^{-4}$ |

[a]HED calculated using Equation A-6 where $C_{ss}$ is the serum concentration associated with the NOAEL or BMDL or the LOAEL if there was no NOAEL or BMDL, $K_e=4.95x10^{-4}$; $V_d=0.2$, and AF=1.
[b]UF of 10 for extrapolation from a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and UF of 10 for human variability.
[c]UF of 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability.

BMDL = lower confidence limit on the BMD; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure; sRBC = sheep red blood cell; UF = uncertainty factor

***Summary of the Principal Study:***

Koskela A, Finnila MA, Korkalainen M, et al. 2016. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicol Appl Pharmacol 301:14-21.

Pregnant C57BL/6/Bk1 mice were exposed to PFOA (96% pure) in food at dose levels of 0 mg/kg/day (n=10) or 0.3 mg/kg/day (n=6) from GD 1 throughout pregnancy (presumed GD 21). PFOA was dissolved in ethanol and applied to palatable food in volumes adjusted according to individual body weights to provide 0.3 mg/kg/day, followed by evaporation of ethanol; controls received food with ethanol applied and then evaporated. It is noted that litter mates of these offspring were examined for neurobehavioral effects in a study conducted by Onishchenko et al. (2011). Groups of five female offspring were sacrificed at either 13 or 17 months of age. The following parameters were used to assess toxicity: body weight and morphometric/biochemical properties in bone (femurs and tibias) of offspring.

As reported in Onishchenko et al. (2011), no differences in dams weight gain, litter size or sex ratio, or pup body weight or brain weight at birth were observed; significant increases in pup liver weight was observed in the PFOA group. Offspring body weight was significantly higher in comparison with controls at 13 and 17 months of age (9.9 and 7.8%, respectively). In 17-month-old offspring, there was a 6.8% increase in periosteal area of the femoral cortical bone and increases in the peri- and endosteal perimeters (3.2 and 5.2%, respectively) and the marrow area (10.0%); an increase in medullary area was also observed. There were no differences in femoral cortical bone area or femoral mineral density. In the tibia, the total area inside the periosteal envelope and the periosteal perimeter were increased (4.9 and 3.5%, respectively). Although the investigators noted in the text that tibial medullary areas were "essentially the same between groups," data in Figure 2 of the paper show a significant increase at 17 months. Significant decreases in tibial mineral density were observed at 13 and 17 months. There

were no significant differences in the tibial medullary area or the endosteal perimeter. There was a trend for increasing maximum force (Fmax); however, the effect was not statistically significant. There were no significant effects on any other measured biochemical parameter in the femur or tibia (stiffness, maximum energy, absorption). Concentrations of PFOA in the femurs and tibias of treated animals were significantly higher (4–5 times) than controls at 13 and 17 months. Koskela et al. (2016) suggested that the PFOA-induced increase in body weight gain may have indirectly affected bone homeostasis, but noted that *in vitro* data provide evidence of a direct effect on osteoblasts and osteoclasts.

***Strengths and Weaknesses:*** The Koskela et al. (2016) study has a number of strengths including examination of several measures of bone status tested at different ages, measurement of bone PFOA levels, and tests to evaluate potential mechanisms of action. To evaluate whether developmental exposure resulted in bone damage in mature animals, the study evaluated bone morphology (periosteal, cortical, and medullary areas and bone mineral density) and bone biomechanical properties (stiffness, maximum force, and maximum energy); all tests were conducted on femur and tibia bone. Measurement at two ages (13 and 17 months) allowed for an evaluation of whether the effect of PFOA on bone changed as the animals aged. The companion *in vitro* study of osteoclasts and osteoblasts provided mechanistic support for the *in vivo* findings. Additionally, the *in vitro* study evaluated four PFOA concentrations and found concentration-related differences.

There are several study limitations that affect the interpretation of the study results; these include the small number of animals tested, use of only one PFOA dose level, inadequate reporting of dietary PFOA levels, and lack of measured serum PFOA levels. Tests of potential alterations in bone mineral density and bone biomechanical properties were only evaluated in 5–6 female offspring per group; however, support for the finding comes from the consistency of the findings at 13 and 17 months of age. The use of only one PFOA dose level does not allow for the establishment of dose-response relationships. This study limitation is mitigated by the extensive intermediate-duration oral exposure database, which allows for an overall assessment of dose-response. The dams were exposed to PFOA dissolved in alcohol and sprayed onto the food pellets. The study did not measure the amount of residual alcohol or the actual amount of PFOA on the food pellets. Koskela et al. (2016) measured PFOA levels in the tibias and femurs but did not measure serum PFOA levels. ATSDR estimated the TWA serum PFOA concentrations using the Wambaugh et al. (2013) model. The lack of measured serum PFOA levels did not allow for validation of whether the model accurately predicted serum levels; the model was validated using data from other intermediate-duration PFOA studies in rats and mice.

***Calculation of Internal Dosimetric:*** TWA serum PFOA concentrations corresponding to external doses and exposure durations were predicted from a pharmacokinetic model (Wambaugh et al. 2013) using animal species-, strain-, and sex-specific parameters (see MRL approach section for details).

***Human Equivalent Dose:*** HEDs were calculated based on the assumption that humans would have similar effects as the laboratory animal at a given serum concentration. HEDs that would result in steady-state serum concentrations of PFOA equal to the serum concentration selected as the POD were calculated using the first-order single-compartment model (see MRL approach section for details).

***Uncertainty Factor:*** The $LOAEL_{HED}$ is divided by a total uncertainty factor of 300:

- 10 for the use of a LOAEL
- 3 for extrapolation from animals to humans with dosimetric adjustment
- 10 for human variability

$MRL = LOAEL_{HED} \div UFs$
$0.000821 \text{ mg/kg/day} \div (10 \times 3 \times 10) = 3 \times 10^{-6} \text{ mg/kg/day}$

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** *In vitro* studies conducted by Kosela et al. (2016) found that at lower concentrations (0.1–10 µM), PFOA stimulated osteoblast differentiation, as evidenced by increased osteocalcin mRNA expression and increased calcium secretion. At higher PFOA levels (>100 µM), osteocalcin expression and calcium secretion were decreased. Lower concentrations of PFOA (0.1–1.0 µM) also increased the number of osteoclasts and increased resorption activity; as with osteoblasts, decreased activity was observed at >100 µM PFOA concentrations.

Epidemiological studies have not evaluated the potential association between serum PFOA levels and impaired development of bone. A small number of studies in adults have examined potential associations with osteoarthritis risk. Innes et al. (2011) reported an elevated risk of physician diagnosed osteoarthritis among adults under 55 years of age with serum PFOA concentrations >13.6 ng/mL; the OR (95% CI) was 1.22 (1.02–1.45) among participants with serum PFOA in the second quartile (13.6–28.0 ng/mL). In a study of NHANES participants, Khalil et al. (2016) found an elevated risk of osteoarthritis among women, OR of 1.84 (1.17–2.90); the mean serum PFOA concentration was 3.7 ng/mL. This study also found in inverse association between serum PFOA and femur neck mineral density in women, but not in men. A second study of NHANES participants also found an elevated risk of osteoarthritis in women with serum PFOA levels of >5.89 ng/mL, OR of 1.98 (1.24–3.19) (Uhl et al. 2013). When segregated by age, an association was found in younger women (20–49 years of age), OR of 4.95 (1.27–19.4), but not among older women (50–84 years of age), OR of 1.33 (0.82–1.16) (Uhl et al. 2013). No association between estimated cumulative exposure to PFOA and the risk of osteoarthritis was observed in an occupational study in which 80% of the cohort was male (Steenland et al. 2015). A discussion of the other findings from epidemiological studies is presented in the MRL introduction section.

***Benchmark Dose Modeling:*** BMD modeling was conducted for the DeWitt et al. (2008) and DeWitt et al. (2016) immunotoxicity studies. Using predicted TWA serum PFOA levels as the internal dosimetric, the IgM response data (summarized in Tables A-9 and A-10) were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.6.0). The following procedure for fitting continuous data was used: the simplest model (linear) was first applied to the data while assuming constant variance; if the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark dose response (BMR). Among all of the models providing adequate fit to the data, the lowest BMDL (the lower limit of a one-sided 95% CI on the BMD) was selected as a reasonably conservative POD when differences between the BMDLs estimated from these models are >2–3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. For both datasets, a BMR of 1 SD change from the control was used.

**Table A-9. T-Cell Independent IgM Antibody Response in C57BL/6N Female Mice Immunized with Sheep Red Blood Cells**

| Number of animals per group | Administered dose (mg/kg/day) | Predicted TWA serum PFOA concentration (µg/mL) | IgM antibody titers[a] [mean serum IgM titer ($log_2$) to reach 0.5 OD] | SE[a] |
|---|---|---|---|---|
| 8 | 0 | 0 | 7.28 | 0.13 |
| 8 | 0.94 | 21.4 | 7.39 | 0.07 |
| 8 | 1.88 | 42.5 | 7.08 | 0.10 |
| 8 | 3.75 | 58.4 | 6.75[b] | 0.09 |
| 8 | 7.5 | 83.5 | 6.61[b] | 0.12 |

[a]Data taken from Figure 3-C using GrabIt.
[b]Statistically different from controls (p<0.05).

PFOA = perfluorooctanoic acid; SE = standard error; TWA = time-weighted-average

Source: DeWitt et al. 2008

**Table A-10. T-Cell Independent IgM Antibody Response In C57BL/6 Female Mice Immunized with Dinitrophenyl-Ficoll**

| Number of animals per group | Administered dose (mg/kg/day) | Predicted TWA serum PFOA concentration (µg/mL) | T-cell independent IgM antibody response[a] [mean serum titer ($log_2$) to reach 0.5 OD] | SD[a] |
|---|---|---|---|---|
| 8 | 0 | 0 | 11.38 | 0.56 |
| 8 | 0.94 | 21.4 | 11.01 | 1.11 |
| 8 | 1.88 | 42.5 | 9.67[b] | 1.34 |
| 8 | 3.75 | 58.4 | 9.81[b] | 1.46 |
| 8 | 7.5 | 83.5 | 9.62[b] | 0.97 |

[a]Data taken from Figure 3b using GrabIt.
[b]Statistically different from controls (p<0.05).

PFOA = perfluorooctanoic acid; SE = standard error; TWA = time-weighted-average

Source: DeWitt et al. 2016

The results of the BMD analysis of the DeWitt et al. (2008) and DeWitt et al. (2016) datasets are presented in Tables A-11 and A-12. For the DeWitt et al. (2008) data, the Hill model with constant variance provided the best fit to the IgM response data, as judged by the model with the lowest AIC since the range of BMDL values were sufficiently close; the fit of this model is presented in Figure A-1. For the DeWitt et al. (2016) IgM response data, constant variance models provided adequate fit; since the estimated BMDL values were not sufficiently close, the model with the lowest BMDL (Exponential 4) was selected; the fit of this model is presented in Figure A-2.

**Table A-11. T-Cell Independent IgM Antibody Response in C57BL/6N Female Mice Immunized With Sheep Red Blood Cells Using Predicted TWA Serum PFOA as the Dose Metric (DeWitt et al. 2008)**

| Model | Test for significant difference p-value[a] | Variance p-value[b] | Means p-value[b] | Scaled residuals[c] Dose below BMC | Scaled residuals[c] Dose above BMC | Scaled residuals[c] Overall largest | AIC | $BMD_{1SD}$ (ng/mL) | $BMDL_{1SD}$ (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|
| **Constant variance** | | | | | | | | | |
| Exponential (model 2)[d] | <0.0001 | 0.46 | 0.08 | 1.73 | 0.72 | 1.73 | -50.41 | ND | ND |
| Exponential (model 3)[d] | <0.0001 | 0.46 | 0.10 | 0.16 | -1.30 | 1.33 | -50.61 | 42.55 | 26.37 |
| Exponential (model 4)[d] | <0.0001 | 0.46 | 0.08 | 1.73 | 0.72 | 1.73 | -50.41 | ND | ND |
| Exponential (model 5)[d] | <0.0001 | 0.46 | 0.36 | -0.14 | 0.09 | 0.67 | -52.34 | 44.11 | 33.33 |
| **Hill[d,e]** | **<0.0001** | **0.46** | **0.41** | **-0.05** | **0.06** | **0.60** | **-52.47** | **43.57** | **33.49** |
| Linear[f] | <0.0001 | 0.46 | 0.09 | 1.69 | 0.67 | 1.69 | -50.66 | ND | ND |
| Polynomial (2-degree)[f] | <0.0001 | 0.46 | 0.08 | 0.10 | -1.41 | 1.43 | -50.00 | ND | ND |
| Polynomial (3-degree)[f] | <0.0001 | 0.46 | 0.08 | 0.10 | -1.41 | 1.43 | -50.00 | ND | ND |
| Polynomial (4-degree)[f] | <0.0001 | 0.46 | 0.08 | 0.10 | -1.41 | 1.43 | -50.00 | ND | ND |
| Power[d] | <0.0001 | 0.46 | 0.10 | 0.16 | -1.32 | 1.35 | -50.49 | 42.62 | 26.23 |

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, the only models that provided adequate fit to the means were the Exponential 3 and 5, Hill, and Power models. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <2–3-fold); therefore, the model with the lowest AIC was selected (Hill).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); ND = not determined, model did not provide adequate fit; PFOA = perfluorooctanoic acid; SD = standard deviation; TWA = time-weighted average

**Figure A-1. Predicted (Hill Model with Constant Variance, 1 Standard Deviation Benchmark Response) and Observed IgM Response Using Predicted TWA Serum PFOA as the Dose Metric**

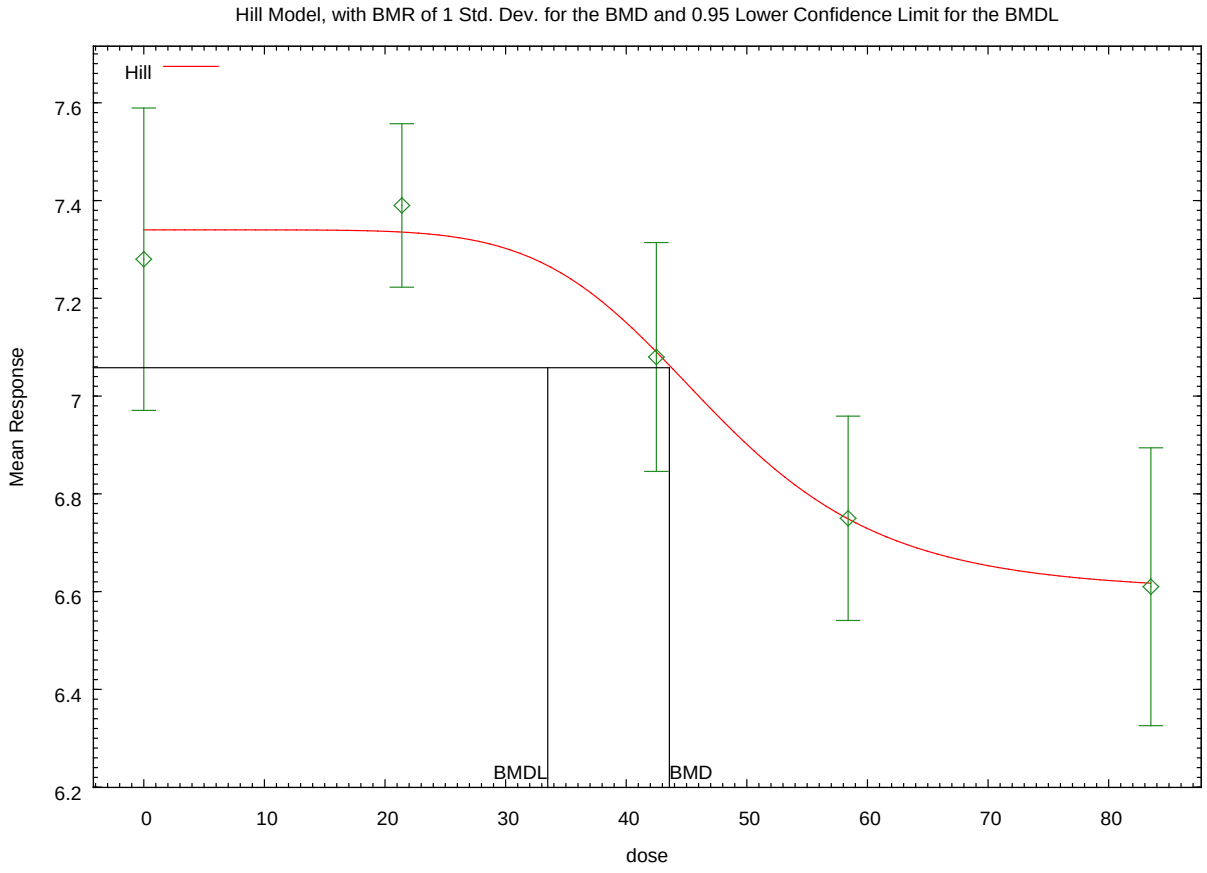


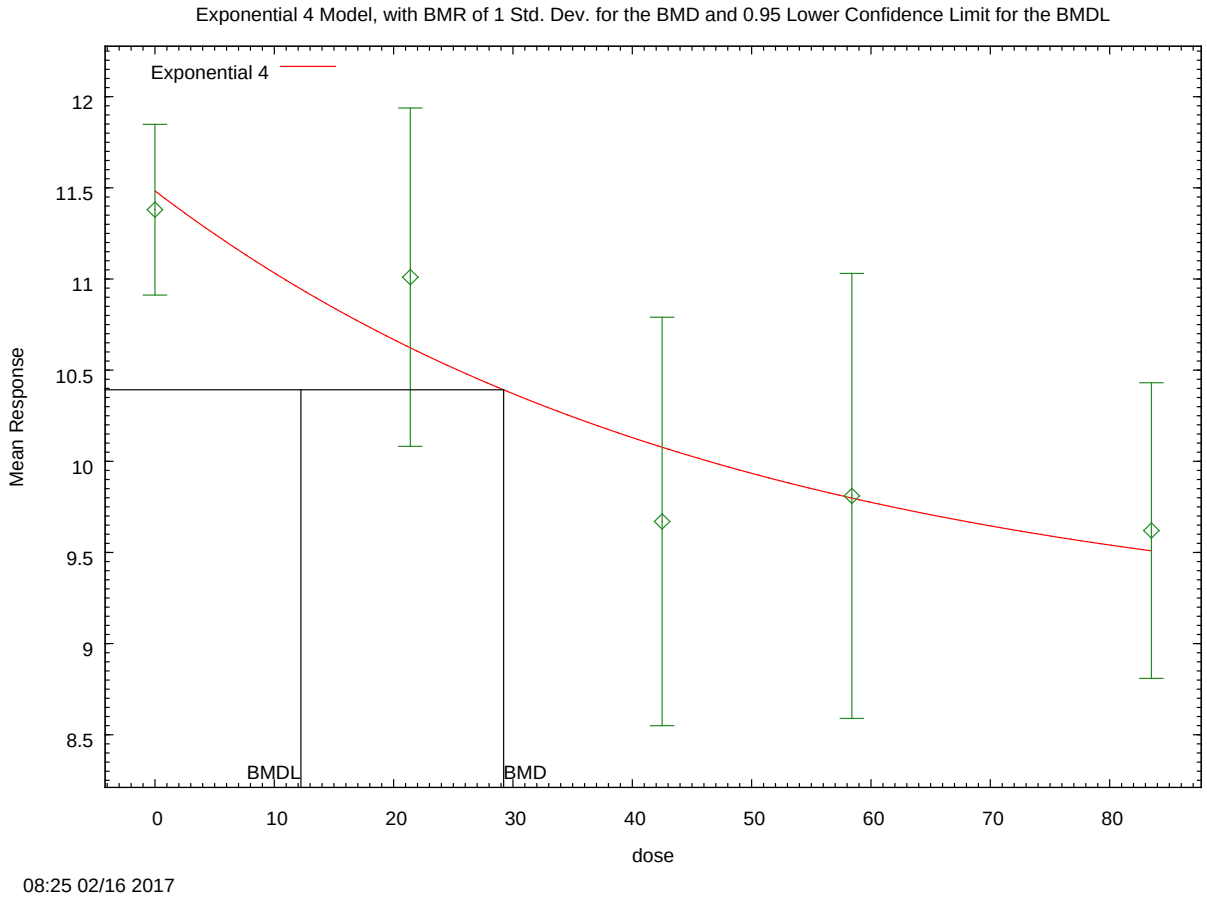
**Table A-12. T-Cell Independent IgM Antibody Response In C57BL/6 Female Mice Immunized With Dinitrophenyl-Ficoll Using Predicted TWA Serum PFOA as the Dose Metric (DeWitt et al. 2016)**

| Model | Test for significant difference p-value[a] | Variance p-value[b] | Means p-value[b] | Scaled residuals[c] Dose below BMC | Scaled residuals[c] Dose above BMC | Scaled residuals[c] Overall largest | AIC | $BMD_{1SD}$ (ng/mL) | $BMDL_{1SD}$ (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|
| **Constant variance** | | | | | | | | | |
| Exponential (model 2)[d] | 0.0029 | 0.12 | 0.34 | -1.47 | -0.17 | -1.47 | 54.00 | 45.00 | 29.56 |
| Exponential (model 3)[d] | 0.0029 | 0.12 | 0.34 | -1.47 | -0.17 | -1.47 | 54.00 | 45.00 | 29.56 |
| **Exponential (model 4)[d,e]** | **0.0029** | **0.12** | **0.31** | **1.01** | **-1.06** | **-1.06** | **54.97** | **29.22** | **12.23** |
| Exponential (model 5)[d] | 0.0029 | 0.12 | 0.71 | 0.00 | -0.08 | 0.29 | 54.76 | 26.62 | 18.75 |
| Hill[d] | 0.0029 | 0.12 | 0.93 | 0.00 | -0.08 | 0.29 | 52.76 | 23.66 | 19.11 |
| Linear[f] | 0.0029 | 0.12 | 0.30 | -1.52 | -0.23 | -1.52 | 54.27 | 47.96 | 32.63 |
| Polynomial (2-degree)[f] | 0.0029 | 0.12 | 0.30 | -1.52 | -0.23 | -1.52 | 54.27 | 47.96 | 32.63 |
| Polynomial (3-degree)[f] | 0.0029 | 0.12 | 0.30 | -1.52 | -0.23 | -1.52 | 54.27 | 47.96 | 32.63 |
| Polynomial (4-degree)[f] | 0.0029 | 0.12 | 0.30 | -1.52 | -0.23 | -1.52 | 54.27 | 47.96 | 32.63 |
| Power[d] | 0.0029 | 0.12 | 0.30 | -1.52 | -0.23 | -1.52 | 54.27 | 47.96 | 32.63 |

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, all models provided adequate fit to the means. BMDLs for models providing adequate fit were not considered to be sufficiently close (differed by >2-fold, but <3-fold). In order to remain conservative, the model with the lowest BMDL was selected (Exponential 4).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable (BMDL computation failed); SD = standard deviation; TWA = time-weighted average

**Figure A-2. Predicted (Exponential 4 Model with Constant Variance, 1 Standard Deviation Benchmark Response) and Observed IgM Response Using Predicted TWA Serum PFOA as the Dose Metric**




***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanoic acid (PFOA)
***CAS Numbers:*** 335-67-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** ATSDR did not identify an adequate study with an exposure duration of ≥365 days. Although adequate data are available for intermediate-duration exposure, ATSDR does not extrapolate across exposure duration.

***Rationale for Not Deriving an MRL:*** The chronic oral animal database for PFOA is limited to dietary exposure studies in male and female rats (3M 1983; Butenhoff et al. 2012c) or male rats (Biegel et al. 2001). The lowest LOAEL identified in the Butenhoff et al. (2012c; 3M 1983) study was 1.5 mg/kg/day for inflammation of salivary gland in male rats exposed to PFOA in the diet for 2 years. At 15 mg/kg/day, hepatocellular necrosis was observed after 1 year of exposure and vascular mineralization was observed in the testes. In the Biegel et al. (2001) study, exposure to 13.6 mg/kg/day PFOA in the diet for 2 years resulted in decreases in body weight gain, increases in Leydig cell hyperplasia, and pancreatic acinar cell hyperplasia in male rats.

The chronic-duration database for PFOA was not considered adequate for MRL derivation due to uncertainty in the selection of the critical effect. The Butenhoff et al. (2012c) study identified the salivary gland as the most sensitive target, but these alterations were only observed in males and may have been due to an antemortem viral infection. Intermediate-duration oral studies have suggested that the immune system is a sensitive target of toxicity in mice; however, potential alterations in immune function have not been investigated in chronic-duration studies; the Butenhoff et al. (2012c) study did conduct histological examinations of immune tissues.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctane sulfonic acid (PFOS)
***CAS Numbers:*** 1763-23-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFOS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFOS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctane sulfonic acid (PFOS)
***CAS Numbers:*** 1763-23-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFOS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFOS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctane sulfonic acid (PFOS)
***CAS Numbers:*** 1763-23-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFOS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFOS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctane sulfonic acid (PFOS)
***CAS Numbers:*** 1763-23-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFOS.

***Rationale for Not Deriving an MRL:*** An acute-duration oral MRL for PFOS cannot be derived because the modeling approach used for estimating HEDs cannot be used to estimate acute human exposure where the exposure duration of 14 days is <1% of the PFOS elimination half-life in humans.

A number of studies have examined the toxicity of PFOS in laboratory animals following acute-duration exposure. The available data suggest that the liver, developing organism, and immune system are sensitive targets. The liver effects consisted of decreases in serum lipids, increases in liver weight, and hepatocellular hypertrophy (Elcombe et al. 2012a, 2012b; Era et al. 2009; Fuentes et al. 2006; Haughom and Spydevold 1992; Vetvicka and Vetvickova 2013; Wan et al. 2011); using the Hall et al. (2012) criteria (see Section 2.9 for a discussion of the criteria) for assessing the adversity of liver alterations for peroxisome proliferators, these effects were not considered relevant for human risk assessment. Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight, hepatocellular hypertrophy, and alterations in serum lipid levels observed in rats and mice, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs. A decrease in serum HDL cholesterol levels was also observed in male and female monkeys receiving three doses of 13.3 or 14 mg/kg/day (TWA dose in males and females, respectively) over 315 days (Chang et al. 2017).

Immunological effects included altered responses to sRBC and decreased IgM antibody formation in response to antigen exposure in mice (Vetvicka and Vetvickova 2013; Zheng et al. 2009). Developmental effects consisted of decreases in neonatal survival (Abbott et al. 2009; Grasty et al. 2003), increases in post-implantation losses (Lee et al. 2015a), decreases in fetal body weight (Case et al. 2001; Era et al. 2009; Fuentes et al. 2007b; Lee et al. 2015a), increases in malformations (Era et al. 2009), and alterations in motor activity (Hallgren et al. 2015; Johansson et al. 2008). The lowest LOAEL identified was 0.5 mg/kg/day for increased post-implantation losses in mice (Lee et al. 2015a). A summary of the adverse effect levels for the immunological and developmental effects are presented in Table A-13.

**Table A-13. Summary of the Adverse Effects Observed in Laboratory Animals Following Acute-Duration Oral Exposure to PFOS**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| ***Immunological*** | | | | |
| Mouse 7 days | | 5 | Impaired response to T-cell mitogens; suppressed response to sRBC | Zheng et al. 2009 |
| Mouse 7 days | | 20 | Inhibition of T lymphocyte proliferation in response to sRBC; decreased phagocytosis by peripheral blood cells and NK cell activity; decreased IgM antibody formation in response to OVA | Vetvicka and Vetvickova 2013 |
| ***Developmental*** | | | | |
| Mouse GDs 11–16 | | 0.5 | Increased post-implantation losses | Lee et al. 2015a |
| Mouse Once | | 0.75 | Decreased motor activity | Johansson et al. 2008 |
| Rabbit GDs 6–20 | 1 | 2.5 | Decreased fetal body weight | Case et al. 2001 |
| Mouse GDs 15–18 | | 4.5 | Decreased number of live pups per litter on PND 15 | Abbott et al. 2009 |
| Mouse GDs 12–18 | | 6 | Reduced pup body weight on PNDs 4 and 8 | Fuentes et al. 2007b |
| Mouse Once | | 11.3 | Altered spontaneous behavior in pups | Hallgren et al. 2015 |
| Rat GDs 19–20 | | 25 (SLOAEL) | Decreased neonatal survival | Grasty et al. 2003 |
| Rat GDs 2–5, 6–9, 10–13, 14–17, or 17–20 | | 25 (SLOAEL) | Decreased neonatal survival | Grasty et al. 2003 |
| Mouse GDs 11–15 | | 50 | Cleft palate and reduced fetal body weight | Era et al. 2009 |

[a]Unless otherwise noted, the LOAEL is for a less serious effect.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NK = natural killer; NOAEL = no-observed-adverse-effect level; perfluorooctane sulfonic acid; PND = postnatal day; SLOAEL = LOAEL for a serious effect; sRBC = sheep red blood cell

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

| | |
|---|---|
| ***Chemical Name*:** | Perfluorooctane sulfonic acid (PFOS) |
| ***CAS Numbers:*** | 1763-23-1 |
| ***Date:*** | March 2020 |
| ***Profile Status:*** | Final |
| ***Route:*** | Oral |
| ***Duration:*** | Intermediate |
| ***MRL:*** | $2x10^{-6}$ mg/kg/day |
| ***Critical Effect:*** | Delayed eye opening and decreased pup body weight |
| ***Reference:*** | Luebker et al. 2005a |
| ***Point of Departure:*** | 0.000515 mg/kg/day |
| ***Uncertainty Factor:*** | 30 |
| ***Modifying Factor:*** | 10 |
| ***LSE Graph Key:*** | 35 |
| ***Species:*** | Rat |

***MRL Summary:*** An intermediate-duration oral MRL of $2x10^{-6}$ mg/kg/day was derived for PFOS based on delayed eye opening and transient decrease in F2 body weight during lactation in the offspring of rats administered PFOS via gavage in a 2-generation study (Luebker et al. 2005a). The MRL is based on a HED NOAEL of 0.000515 mg/kg/day and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) and a modifying factor of 10 for concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity.

***Selection of the Critical Effect:*** Intermediate-duration studies in monkeys, rats, and mice have identified several sensitive targets of PFOS toxicity including the liver, nervous system, immune system, and the developing organism; adverse outcomes occurred in these tissues at lower doses than other effects. The lowest LOAEL and NOAEL values for these outcomes are presented in Table A-14; given the large number of intermediate-duration studies, this table was limited to studies which identified LOAEL values of ≤3 mg/kg/day. The liver effects observed in monkeys, rats, and mice included increases in liver weight, decreases in serum lipids, hepatocellular degeneration, and focal necrosis (Cui et al. 2009; Curran et al. 2008; Elcombe et al. 2012a; Lefebvre et al. 2008; Seacat et al. 2002, 2003; Thibodeaux et al. 2003; Wan et al. 2011; Yahia et al. 2008). In the absence of degenerative changes such as necrosis, the liver hypertrophy observed in rodent studies was not considered relevant to human risk assessment (Hall et al. 2012). Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight, hepatocellular hypertrophy, and alterations in serum lipid levels observed in rats and mice, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs.

Several studies have examined potential neurological endpoints and found overt signs of neurotoxicity (cachexia, lethargy, and tonic convulsions in response to stimuli) in rats exposed to 5 or 8.5 mg/kg/day (Cui et al. 2009; Kawamoto et al. 2011) and impaired spatial learning and memory in mice exposed to 2.15 mg/kg/day (Long et al. 2013). Four studies have evaluated the immune response of PFOS exposed mice following exposure to an antigen (sRBC) or a virus (Dong et al. 2009, 2011; Guruge et al. 2009; Peden-Adams et al. 2008). Although the studies have consistently reported adverse effects, there is considerable overlap in LOAEL values. Peden-Adams et al. (2008) identified the lowest LOAEL of 0.00166 mg/kg/day with a NOAEL of 0.000166 mg/kg/day for a suppressed response to sRBC in mice administered PFOS for 28 days. Longer duration studies (Dong et al. 2009, 2011) have identified NOAEL values (0.0083 and 0.0167 mg/kg/day) in mice exposed to PFOS for 60 days that are higher than

the LOAELs identified in the Peden-Adams et al. (2008) study. It is noted that the studies used different mouse strains (B6C3F1 in the Peden-Adams study and C57BL/6N in the Dong studies), which may account for this difference. A variety of developmental effects have been observed in rats and mice; these include increases in postnatal mortality (Chen et al. 2012b; Lau et al. 2003; Luebker et al. 2005a, 2005b; Xia et al. 2011; Yahia et al. 2008), neurodevelopmental alterations (locomotor activity and impaired learning) (Butenhoff et al. 2009b; Onishchenko et al. 2011; Wang et al. 2015c), developmental delays (Lau et al. 2003; Luebker et al. 2005a), and malformations and anomalies (sternal defects and cleft palate) (Era et al. 2009; Thibodeaux et al. 2003; Yahia et al. 2008). The Wang et al. (2015c) study showed that decreases in spatial learning were observed in rats exposed *in utero* and in rat pups exposed postnatally (PND 7). Other effects that occur at similar doses include decreases in body weight (Lefebvre et al. 2008; Luebker et al. 2005a, 2005b; Seacat et al. 2002) and alterations in thyroid hormone levels (decreases in T3 and T4 levels and increases in TSH levels) (Curran et al. 2008; Luebker et al. 2005b; Thibodeaux et al. 2003).

The most sensitive targets of PFOS toxicity in laboratory animals are similar to those identified in longer term epidemiological studies. These effects include liver damage and increases in serum lipids, decreased antibody response to vaccines, and small decreases in birth weight; epidemiological studies have not consistently found neurological effects to be associated with serum PFOS levels.

**Table A-14. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure to PFOS**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| ***Hepatic*** | | | | |
| Monkey 26 weeks | 0.15 | 0.75 | Increased liver weight, decreased serum cholesterol, hepatocellular hypertrophy, lipid vacuolation | Seacat et al. 2002 |
| ***Neurological*** | | | | |
| Mouse 3 months | 0.43 | 2.15 | Impaired spatial learning and memory | Long et al. 2013 |
| ***Immunological*** | | | | |
| Mouse 28 days | 0.00016 | 0.00166 | Suppressed response to sRBC | Peden-Adams et al. 2008 |
| Mouse 21 days | 0.005 | 0.025 | Decreased resistance to influenza virus | Guruge et al. 2009 |
| Mouse 60 days | 0.0083 | 0.083 | Impaired response to sRBC | Dong et al. 2009 |
| Mouse 60 days | 0.0167 | 0.083 | Impaired response to sRBC | Dong et al. 2011 |
| ***Developmental*** | | | | |
| Mouse GDs 1–21 | | 0.3 | Decreased locomotion, muscle strength, motor coordination in adult offspring | Onishchenko et al. 2011 |
| Rat 84 days | 0.1 | 0.4 | Delayed eye opening | Luebker et al. 2005a |
| Rat 67 days | | 0.4 | Decreased pup weight | Luebker et al. 2005b |

**Table A-14. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure to PFOS**

| Species and exposure duration | NOAEL (mg/kg/day) | LOAEL[a] (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|
| Rat GD 1–PND 1 | | 0.8 | Decreased spatial learning | Wang et al. 2015c |
| Rat GD 0–PND 20 | 0.3 | 1 | Increased locomotor activity and concurrent failure to habituate to test environment in male pups on PND 17 | Butenhoff et al. 2009b |
| Mouse GDs 1–17 | | 1 | Delayed eye opening | Lau et al. 2003 |
| Mouse GDs 0–17 | | 1 | Increased sternal defects | Yahia et al. 2008 |
| Rat GDs 1–21 | 0.1 | 2 | Increased postnatal mortality and severe lung histopathology | Chen et al. 2012b |
| Rat GDs 2–21 | 0.6 | 2 | Increased neonatal mortality | Xia et al. 2011 |

[a]LOAELs for less serious health effects.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NK = natural killer; NOAEL = no-observed-adverse-effect level; PFOS = perfluorooctane sulfonic acid; PND = postnatal day; sRBC = sheep red blood cell

***Selection of the Principal Study:*** Using the Wambaugh et al. (2013) pharmacokinetic model, TWA serum concentrations corresponding to external doses (mg/kg/day) and exposure durations (days) were predicted for the studies listed in Table A-14. Pharmacokinetic model parameters were not available for C57BL/6N mice, B6C3F1 mice, or Wistar rats, which precluded predicting TWA serum concentrations for the Long et al. (2013), Dong et al. (2009, 2011), Guruge et al. (2009), Peden-Adams et al. (2008), Wang et al. (2015c), Onishchenko et al. (2011), and Yahia et al. (2008) studies. The predicted serum PFOS levels for each administered dose is presented in Table A-15.

**Table A-15. Summary of the Predicted TWA Serum PFOS levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Predicted TWA serum PFOS (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| ***Hepatic*** | | | | |
| Cynomolgus Monkey 26 weeks | 0.03 (males) | 7.81 | Increased liver weight, decreased serum cholesterol, hepatocellular hypertrophy, mild bile stasis, lipid vacuolation at 0.75 mg/kg/day | Seacat et al. 2002 |
| | 0.15 (males) | 37.8 | | |
| | 0.75 (males) | 150 | | |
| | 0.03 (females) | 7.72 | | |
| | 0.15 (females) | 37.6 | | |
| | 0.75 (females) | 146 | | |

**Table A-15. Summary of the Predicted TWA Serum PFOS levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Predicted TWA serum PFOS (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| ***Neurological*** | | | | |
| C57BL/6 Mouse 3 months | 0.43<br>2.15<br>10.75 | Not calculated | Impaired spatial learning and memory at 2.15 mg/kg/day | Long et al. 2013 |
| ***Immunological*** | | | | |
| B6C3F1 Mouse 28 days | 0.00016<br>0.00166<br>0.00331<br>0.0166<br>0.0331 | Not calculated[a] | Suppressed response to sRBC at 0.00166 mg/kg/day | Peden-Adams et al. 2008 |
| B6C3F1 Mouse 21 days | 0.005<br>0.025 | Not calculated[a] | Decreased resistance to influenza virus at 0.025 mg/kg/day | Guruge et al. 2009 |
| C57BL/6N Mouse 60 days | 0.0083<br>0.083<br>0.41667<br>0.8333<br>2.0833 | Not calculated[a] | Impaired response to sRBC at 0.083 mg/kg/day | Dong et al. 2009 |
| C57BL/6N Mouse 60 days | 0.0083<br>0.0167<br>0.083<br>0.41667<br>0.8333 | Not calculated[a] | Impaired response to sRBC at 0.083 mg/kg/day | Dong et al. 2011 |
| ***Developmental*** | | | | |
| C57BL/6 Mouse GDs 1–21 | 0.3 | Not calculated | Decreased locomotion, muscle strength, motor coordination in adult offspring at 0.3 mg/kg/day | Onishchenko et al. 2011 |
| Sprague-Dawley Rat 84 days | 0.1<br>0.4<br>1.6<br>3.2 | 7.43<br>29.7<br>119<br>238 | Delayed eye opening in F1 pups and transient decrease in F2 pup body weight during lactation at 0.4 mg/kg/day | Luebker et al. 2005a |
| Sprague-Dawley Rat 67 days | 0.4<br>0.8<br>1<br>1.2<br>1.6<br>3.2 | 24.1<br>48.1<br>60.1<br>72.2<br>96.2<br>120 | Decreased pup weight per litter at birth and on LD 5 at 0.4 mg/kg/day | Luebker et al. 2005b |

**Table A-15. Summary of the Predicted TWA Serum PFOS levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Predicted TWA serum PFOS (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| Wistar Rat GD 1–PND 1 | 0.8 | Not calculated[b] | Decreased spatial learning at 0.8 mg/kg/day | Wang et al. 2015c |
| Sprague-Dawley Rat GD 0–PND 20 | 0.1<br>0.3<br>1 | 3.75<br>11.3<br>37.5 | Increased locomotor activity and concurrent failure to habituate to test environment in male pups on PND 17 at 1 mg/kg/day | Butenhoff et al. 2009b |
| CD-1 Mouse GDs 1–17 | 1<br>5<br>10<br>15<br>20 | 31.9<br>146<br>216<br>244<br>260 | Delayed eye opening at 1 mg/kg/day | Lau et al. 2003 |
| ICR Mouse GDs 0–17 | 1 | Not calculated | Increased sternal defects at 1 mg/kg/day | Yahia et al. 2008 |
| Sprague-Dawley Rat GDs 1–21 | 0.1<br>2 | 2.01<br>40.1 | Increased postnatal mortality and severe lung histopathology at 2 mg/kg/day | Chen et al. 2012b |
| Sprague-Dawley Rat GDs 2–21 | 0.1<br>0.6<br>2 | 1.92<br>11.5<br>38.3 | Increased neonatal mortality at 2 mg/kg/day | Xia et al. 2011 |

[a]See Table A-17 for measured serum PFOS concentrations.
[b]Reported serum PFOS concentrations of 25.7 and 64.3 µg/mL in dams on PND 7 and 35, respectively.

GD = gestation day; LD = lactation day; PFOS = perfluorooctane sulfonic acid; PND = postnatal day; sRBC = sheep red blood cell; TWA = time-weighted average

***Selection of the Point of Departure for the MRL:*** None of the studies with predicted serum PFOS levels had datasets that were amenable for BMD modeling; thus, the NOAEL/LOAEL approach was used to identify PODs for derivation of the intermediate-duration MRL for PFOS. A summary of the PODs is presented in Table A-16. HEDs were calculated for each potential POD (NOAEL or LOAEL) identified in laboratory animal studies using the first-order single-compartment model previously discussed and the assumption that humans would have similar effects as the laboratory animal at a given serum concentration. The HEDs for each POD are presented in Table A-16. The potential $POD_{HED}$ values were divided by a total uncertainty factor to calculate candidate MRLs; these values are also presented in Table A-16. The lowest administered doses associated with adverse effects were found in the immunotoxicity studies conducted by Dong et al. (2009, 2011), Guruge et al. (2009), and Peden-Adams et al. (2008). These data could not be considered as PODs because TWA serum PFOS values could not be predicted due to the lack of pharmacokinetic model parameters for the two mouse strains tested. Although there is considerable overlap between the LOAEL for IgM response to sRBC (0.00166 mg/kg/day) identified in the Peden-Adams et al. (2008) 28-day study and the NOAELs for IgM

response to sRBC (0.0083 and 0.0167 mg/kg/day) identified in the Dong et al. (2009, 2011) 60-day studies, the data do suggest that immunotoxicity could occur at <0.3 mg/kg/day (the lowest LOAEL identified in developmental toxicity studies).

**Table A-16. Summary of Potential Points of Departures Human Equivalent Doses ($POD_{HED}$) for Intermediate-Duration Oral MRL for PFOS**

| Endpoint (reference) | Predicted serum concentrations (µg/mL) NOAEL | LOAEL | $POD_{HED}$[a] (mg/kg/day) | Total UF | Candidate MRLs (mg/kg/day) |
|---|---|---|---|---|---|
| Increased rat pup mortality and lung histopathology (Chen et al. 2012b) | 2.01 | 40.1 | 0.000139 | 300[b] | $4.6x10^{-7}$ |
| Decreased rat pup weight at birth and on PND 4 (Luebker et al. 2005b) | | 24.1 | 0.00167 | 3,000[c] | $5.6x10^{-7}$ |
| Delayed eye opening in mouse pups (Lau et al. 2003) | | 31.9 | 0.00221 | 3,000[c] | $7.4x10^{-7}$ |
| Neurodevelopmental effects in male rat pups (Butenhoff et al. 2009b) | 11.3 | 37.5 | 0.000780 | 300[b] | $2.6x10^{-6}$ |
| Delayed eye opening and decreased F2 rat pup body weight (Luebker et al. 2005a) | 7.43 | 29.7 | 0.000515 | 300[b] | $1.7x10^{-6}$ |
| Increased neonatal mortality in rat pups (Xia et al. 2011) | 11.5 | 38.3 | 0.000797 | 300[b] | $2.7x10^{-6}$ |
| Hepatic effects in monkeys (Seacat et al. 2002) | 37.8 | 150 | 0.00262 | 300[b] | $8.7x10^{-6}$ |

[a]HED calculated using Equation A-6 where $C_{ss}$ is the serum concentration associated with the NOAEL or BMDL or the LOAEL if there was no NOAEL or BMDL, $K_e=3.74x10^{-4}$; $V_d=0.2$, and AF=1.
[b]UFs of 3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability and modifying factor (MF) of 10 for concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity.
[c]UF of 10 for extrapolation from a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and UF of 10 for human variability and MF of 10 for concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity.

BMDL = lower limit on the benchmark dose; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; PFOS = perfluorooctane sulfonic acid; PND = postnatal day; UF = uncertainty factor

The serum PFOS concentrations predicted to occur at the lowest LOAEL values were 24.1, 29.7, and 31.9 µg/mL identified in the Luebker et al. (2005b), Luebker et al. (2005a), and Lau et al. (2003) studies; decreases in pup body weight and delays in eye opening were observed at these levels. Luebker et al. (2005a) was the only study that identified a NOAEL for these effects. The predicted serum concentration for this NOAEL dose was selected as the basis for the MRL.

***Summary of the Principal Study:***

Luebker DJ, Case MT, York RG, et al. 2005a. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicol 215:126-148.

Groups of Sprague-Dawley rats (P generation) (35/sex/dose level) were administered PFOS (86.9% pure) by gavage in deionized water with 2% Tween-80 at doses of 0, 0.1, 0.4, 1.6, or 3.2 mg/kg/day for 6 weeks before mating and until sacrifice (after mating for males, GD 10 for some females, and PND 21 for the remaining females). Body weight and feed consumption were evaluated during the dosing period. Prior to mating, 15 females per dose group were evaluated for estrous cycling. Ten females/dose group were sacrificed on GD 10 and the remaining females were allowed to give birth (F1 generation). Parental rats sacrificed on GD 10 were examined for number of corpora lutea, implantations, and viable and non-viable fetuses. Body weight of F1 was evaluated during lactation; also, F1 rats were assessed for developmental landmarks during lactation. On PND 22, the F1 rats were started on the same diet as the parental rats. At approximately PND 90, F1 were mated to produce the F2 generation. F1 males and females were killed as the P generation. F1 females and males were evaluated for vaginal patency and preputial separation, respectively. At age 24 days, F1 rats were administered three neurobehavioral tests (learning, memory retention, and avoidance memory). At the age of 70 days, F1 were administered three different neurobehavioral tests (neuromuscular coordination, swimming ability, learning, and memory). PFOS was analyzed in liver and blood from parental females and in liver from F1on PND 21; and in liver and serum from parental males after mating and after 42–56 days of dosing.

There were no deaths in parental males or females and no clinical signs in parental males. High-dose parental males had significantly reduced terminal body weight (11% reduction). Absolute and relative food consumption was reduced during treatment in males by less than 10%. Parental females at 0.4 mg/kg/day and higher had localized areas of partial alopecia. Body weight of parental females in the 3.2 mg/kg/day group was significantly lower during cohabitation and gestation (11% reduced). Absolute and relative food consumption were significantly reduced in 3.2 mg/kg/day parental females during premating and gestation (>15%) and in 1.6 mg/kg/day parental females during lactation. Administration of PFOS did not affect any mating or fertility parameter. Estrous cycling was not affected. Examination of parental females sacrificed on GD 10 showed no significant effect on numbers of corpora lutea or implantations or viable and non-viable fetuses. Significant delivery observations for 3.2 mg/kg/day parental females included reduced number of implantations per delivered litter, decreased gestational length, increased number of dams with all pups dying on PNDs 1–4 (also at 1.6 mg/kg/day). Observation of F1 pups during PNDs 1–21 showed significantly reduced weight and decreased viability (≥1.6 mg/kg/day). Examination of dead F1 pups did not reveal a cause of death; no labored breathing was noted in pups at birth. Developmental delays were noted at 1.6 mg/kg/day (pinna unfolding, surface righting, and air righting), and 0.4 mg/kg/day (eye opening). The investigators noted that the delay in eye opening was not considered an adverse outcome but did not provide a rationale for this conclusion. Follow-up observations of 0.1 and 0.4 mg/kg/day offspring showed no alterations in body weight or food consumption, including F1 females during gestation and lactation. Sexual maturation was not affected in F1 males or females; no effects were noted in the neurobehavioral tests. Reproductive performance of F1 were not affected. Viability of F2 pups during PNDs 1–21 was not affected. F2 pup weight was significantly reduced at 0.4 mg/kg/day on PND 7 (13%) and PND 14 (9.6%). The investigators noted that the decrease in pup weight was not considered toxicologically relevant and may have been due to minimally larger live litter sizes, as compared to the control group, and that there were no differences on PND 21. ATSDR notes that there were no significant differences in pup body weight between the control group and the 0.4 mg/kg/day group on PND 4 prior to culling and after culling, and considers the delay in eye opening to be toxicologically relevant. Serum and liver PFOS increased with dose.

***Strengths and Weaknesses:*** The Luebker et al. (2005a) study is a well-designed 2-generation study evaluating a number of reproductive and developmental endpoints in adequate number of animals. The study was designed to evaluate four PFOS dose levels administered prior to mating and during mating, gestation, and lactation across two generations. The test included a number of parameters to assess reproductive performance (mating, estrous cycling, and fertility), reproductive outcomes (gestation length, number of implantation sites, stillbirths), and neonatal toxicity (survival and body weight). The experiment also included a cross-foster study, which allowed for the evaluation of whether neonatal effects were due to maternal care/maternal toxicity or to a direct effect on the pups. An additional strength of the study is that it evaluated several endpoints (e.g., lung morphology and lung glycogen stores) that could elucidate the mechanisms of action for fetal deaths. Luebker et al. (2005a) measured serum and liver PFOS levels, which allowed for validation of the Wambaugh et al. (2013) model's predicted serum TWA PFOS level. Although the study was designed to evaluate four PFOS dose levels, high mortality in the F1 offspring at the two highest dose levels resulted in a discontinuation of these dose levels, which limits the amount of data that can be used to establish dose-response relationships.

***Calculations of Internal Dosimetric:*** TWA serum PFOS concentrations corresponding to external doses and exposure durations were predicted from a pharmacokinetic model (Wambaugh et al. 2013) using animal species-, strain-, and sex-specific parameters (see MRL approach section for details).

***Human Equivalent Dose:*** HEDs were calculated based on the assumption that humans would have similar effects as the laboratory animal at a given serum concentration. HEDs that would result in steady-state serum concentrations of PFOS equal to the serum concentration selected as the POD were calculated using the first order single-compartment model (see MRL approach section for details).

***Uncertainty Factor and Modifying Factor:*** The $NOAEL_{HED}$ is divided by a total uncertainty factor (UF) of 30 and modifying factor (MF) of 10:

- 3 UF for extrapolation from animals to humans with dosimetric adjustment
- 10 UF for human variability
- 10 MF for concern that immunotoxicity may be a more sensitive endpoint of PFOS toxicity than developmental toxicity

$MRL = NOAEL_{HED} \div (UFs \times MF)$
$0.000515 \text{ mg/kg/day} \div ((3 \times 10) \times 10) = 2 \times 10^{-6} \text{ mg/kg/day}$

Although pharmacokinetic model parameters were not available for the strain/sex of the animals tested in the immunotoxicity studies, most of the studies did provide measured serum PFOS levels. The serum PFOS levels at the NOAEL and LOAEL doses are presented in Table A-17. The measured serum PFOS levels associated with altered immune responses are approximately 1–10 times lower than the serum concentration predicted to occur at the NOAEL dose. These data suggest that immunotoxicity may be a more sensitive effect than developmental toxicity.

**Table A-17. Measured Serum PFOS Levels at the NOAEL and LOAEL Doses for Immunological Effects**

| Effect, species and exposure duration | | Dose (mg/kg/day) | Measured mean serum PFOS (µg/mL) | Reference |
|---|---|---|---|---|
| Impaired response to sRBC in mice exposed for 60 days | NOAEL | 0.0083 | 0.674 | Dong et al. 2009 |
| | LOAEL | 0.083 | 7.132 | |

**Table A-17. Measured Serum PFOS Levels at the NOAEL and LOAEL Doses for Immunological Effects**

| Effect, species and exposure duration | | Dose (mg/kg/day) | Measured mean serum PFOS (µg/mL) | Reference |
|---|---|---|---|---|
| Impaired response to sRBC in mice exposed for 60 days | NOAEL | 0.0167 | 2.36 | Dong et al. 2011 |
| | LOAEL | 0.083 | 10.75 | |
| Decreased resistance to influenza virus in mice exposed for 21 days | NOAEL | 0.005 | 0.189 | Guruge et al. 2009 |
| | LOAEL | 0.025 | 0.670 | |
| Suppressed response to sRBC in mice exposed for 28 days | NOAEL | 0.00016 | 0.0178 | Peden-Adams et al. 2008 |
| | LOAEL | 0.00166 | 0.0915 | |

PFOS = perfluorooctane sulfonic acid; sRBC = sheep red blood cell

A candidate MRL was calculated using the NOAEL of 0.0167 mg/kg/day identified in the Dong et al. (2011). This study was selected over the other immunotoxicity studies because it identified the highest NOAEL for immunotoxicity and it had the longest exposure duration; the Peden-Adams et al. (2008) was not selected because the LOAEL of 0.00166 mg/kg/day is not supported by the other three studies. A TWA concentration was estimated using a similar approach described for PFHxS and PFNA in the MRL approach section. The estimated TWA concentration was 1.2 µg/mL for the 0.0167 mg/kg/day; this estimated TWA concentration was used to calculate a HED of 0.000083 mg/kg/day. A candidate MRL of $3x10^{-6}$ was calculated using an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability). This MRL is similar to the MRL calculated from the Luebker et al. (2005a) study and lends support to using the additional modifying factor of 10 to account for the lack of pharmacokinetic modeling parameters for the mouse strains tested for immunotoxicity.

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** A discussion of the findings from epidemiological studies is presented in the MRL introduction section.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctane sulfonic acid (PFOS)
***CAS Numbers:*** 1763-23-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** ATSDR did not identify an adequate study with an exposure duration of ≥365 days. Although adequate data are available for intermediate-duration exposure, ATSDR does not extrapolate across exposure duration.

***Rationale for Not Deriving an MRL:*** Immune function was not examined following chronic-duration oral exposure in laboratory animal studies; the only chronic-duration oral study (Butenhoff et al. 2012b; Thomford 2002b), did not find histological alterations in immune tissues (lymph nodes, spleen, and thymus) in rats at doses as high as 1.04 mg/kg/day. Impaired immune function was the most sensitive endpoint in intermediate-duration mouse studies. Given the concern that immunotoxicity may occur at lower doses than liver toxicity, a chronic-duration oral MRL for PFOS is not recommended at this time.

One study has evaluated the chronic toxicity of PFOS in laboratory animals. Histological alterations in the liver were the primary effects observed in rats exposed to PFOS in the diet for 2 years (Butenhoff et al. 2012b; Thomford 2002b). Centrilobular hepatocellular hypertrophy was observed in rats exposed to ≥0.1 mg/kg/day. At 1.04 mg/kg/day, increases in the incidence of single cell necrosis and cystic degeneration were observed in the liver. Decreases in body weight were observed at 1.04 mg/kg/day in female rats. Thus, the 1.04 mg/kg/day dose was identified as the lowest LOAEL for this study. Epidemiological data (Dalsager et al. 2016; Dong et al. 2013; Fei et al. 2010; Grandjean et al. 2012, 2016; Granum et al. 2013; Kielsen et al. 2016; Mogensen et al. 2015a; Stein et al. 2016a; Zhu et al. 2016) suggest that the immune system is a sensitive target of PFOS toxicity following long-term exposures, which is supported by intermediate-duration PFOS laboratory animal studies (Dong et al. 2009, 2011; Guruge et al. 2009; Peden-Adams et al. 2008).

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexane sulfonic acid (PFHxS)
***CAS Numbers:*** 355-46-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFHxS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFHxS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexane sulfonic acid (PFHxS)
***CAS Numbers:*** 355-46-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFHxS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFHxS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexane sulfonic acid (PFHxS)
***CAS Numbers:*** 355-46-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFHxS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFHxS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexane sulfonic acid (PFHxS)
***CAS Numbers:*** 355-46-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFHxS.

***Rationale for Not Deriving an MRL:*** The acute oral database for PFHxS was not considered adequate for derivation of an MRL due to the short duration of the only available study and the lack of pharmacokinetic model parameters for calculating an HED.

In the only available study of PFHxS in laboratory animals, Viberg et al. (2013) reported altered spontaneous behavior and habituation in adult mice administered a single gavage dose of 9.2 mg/kg/day PFHxS on PND 10; no alterations were observed at 6.1 mg/kg/day. This single exposure study was not considered adequate as the basis of an acute-duration MRL for PFHxS due to the uncertainty of whether an MRL based on this study would be protective for repeated exposures or for other potential sensitive endpoints, such as immunotoxicity.

For perfluoroalkyls, ATSDR has used the approach of predicting TWA serum perfluoroalkyl levels in laboratory animals and calculating HEDs for these serum concentrations. For PFOA and PFOS, the Wambaugh et al. (2013) pharmacokinetic model was utilized for predicting the TWA serum perfluoroalkyl concentrations. However, strain-, sex-, and compound-specific model parameters are not available for other perfluoroalkyls, thus precluding deriving MRLs for other perfluoroalkyls. Other approaches such as “read across” (i.e., using data for a particular endpoint from one chemical to predict the same endpoint for another chemical that has similar chemical structure or mechanisms of action) or equivalency factors were considered for the other perfluoroalkyls; however, there are limited data available that would allow for comparison of the toxicity and toxicokinetic properties of different perfluoroalkyls. Peters and Gonzalez (2011) noted that the toxic equivalency factor approach would not be suitable for perfluoroalkyls because the current data suggest that the toxicity of these compounds appear to be mediated by multiple receptors, including PPARα, CAR, and PXR, and that there may be species differences in the response mediated by different receptors. Additionally, available data suggest that there are qualitative differences in the toxicities of various perfluoroalkyls.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexane sulfonic acid (PFHxS)
***CAS Numbers:*** 355-46-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate
***MRL:*** $2x10^{-5}$ mg/kg/day
***Critical Effect:*** Thyroid follicular epithelial hypertrophy/hyperplasia
***Reference:*** Butenhoff et al. 2009a
***Point of Departure:*** 0.0047 mg/kg/day
***Uncertainty Factor:*** 30
***Modifying Factor:*** 10
***LSE Graph Key:*** 33
***Species:*** Rat

***MRL Summary:*** An intermediate-duration oral MRL of $2x10^{-5}$ mg/kg/day was derived for PFHxS based on thyroid follicular epithelial hypertrophy/hyperplasia in adult male rats administered via gavage PFHxS for a minimum of 42 days (Butenhoff et al. 2009a). The MRL is based on a HED NOAEL of 0.0047 mg/kg/day and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) and a modifying factor of 10 for database limitations.

***Selection of the Critical Effect:*** Four intermediate-duration studies in laboratory animals have been identified for PFHxS. In a developmental toxicity study, increased incidences of thyroid follicular cells hypertrophy/hyperplasia were observed in F0 male rats administered ≥3 mg/kg/day (Butenhoff et al. 2009a). Increased liver weight and centrilobular hepatocellular hypertrophy were also observed in the males at ≥3 mg/kg/day. Consistent with the Hall et al. (2012), the liver effects were not considered a relevant endpoint for humans. Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight and hepatic lipid levels and alterations in serum lipid levels observed in rats and mice, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs.

No reproductive or developmental effects were reported in the Butenhoff et al. (2009a) study. A second developmental toxicity study reported decreases in serum thyroxine levels in rat dams and pups administered 5 mg/kg/day PFHxS on GDs 7–22 (Ramhøj et al. 2018); no alterations in pup birth weight or weight gain were observed. In a 1-generation reproductive/developmental toxicity study, decreases in the number of pups per litter were observed in the offspring of mice administered 1 mg/kg/day (Chang et al. 2018). At 3 mg/kg/day, single cell necrosis and microvascular fatty changes were observed at 3 mg/kg/day. Liver effects (decreases in serum lipids, increases in hepatic triglyceride levels, and increases in liver weight) were also observed in mice exposed to 6 mg/kg/day PFHxS in the diet for 4–6 weeks (Bijland et al. 2011) and mice administered 0.3 mg/kg/day (Chang et al. 2018). Using the Hall et al. (2012) criteria (see Section 2.9 for a discussion of the criteria), the liver effects were not considered relevant for human risk assessment. Thus, the lowest LOAEL identified in intermediate-duration studies was 3 mg/kg/day for thyroid effects.

There is some uncertainty regarding the selection of thyroid alterations as the critical effect. Butenhoff et al. (2009a) suggested that the histological alterations in the thyroid may be secondary to the liver effects

(hepatocellular hypertrophy). The alteration may be due to binding competition between PFHxS and thyroid hormones and possible induction of thyroid hormone metabolism by the liver. Ramhøj et al. (2018) reported decreases in serum T4 levels but did not evaluate possible thyroid gland histological alterations. The Chang et al. (2018) 1-generation reproduction study did not find alterations in serum TSH levels in mice.

A limited number of epidemiological studies have examined potential thyroid effects. Two epidemiological studies have examined thyroid disease associated with PFHxS exposure (Chan et al. 2011; Wen et al. 2013); one study found increased risk of subclinical hypothyroidism and subclinical hyperthyroidism among women (Wen et al. 2013) and the second study did not find an increased risk of hypothyroxinemia (Chan et al. 2011). The small number of studies precludes evaluating the possible association between PFHxS exposure and thyroid disease in humans. A meta-analysis of epidemiological data (Kim et al. 2018) found an inverse correlation between serum PFHxS levels and total T4 levels in the general population; there was no correlation among pregnant women. No associations were found for free T4, total T3, or TSH.

Species-related differences in thyroid parameters between rats and humans also add to the uncertainty. Some differences include higher rate of T4 production in rats than in humans, and very low levels of thyroxine binding globulin compared to high levels in humans, and sex-related differences in serum TSH levels (higher levels in males compared to females) in rats, but not in humans (Choksi et al. 2003). It is not known if these species differences would influence the relative toxicity of PFHxS.

***Selection of the Principal Study:*** Since the liver effects were not considered relevant to humans, the lowest LOAEL identified for PFHxS was 1 mg/kg/day for decreases in the number of pups per litter identified in the Chang et al. (2018) study. The investigators noted that the toxicological significance of this alteration was uncertain because there was no clear dose-response and no alterations in the number of implantation sites, number of viable pups, or pup to implant ratios. Thus, the Butenhoff et al. (2009a) study, which reported thyroid effects in male rats at LOAEL of 3 mg/kg/day, with a NOAEL of 1 mg/kg/day, was selected as the principal study.

***Summary of the Principal Study:***

Butenhoff JL, Chang SC, Ehresman DJ, et al. 2009a. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reprod Toxicol 27:331-341. (Results from this study are also reported in Hoberman and York 2003.)

The reproductive/developmental effects of PFHxS were studied in Sprague-Dawley rats (15/sex/group). Doses of 0, 0.3, 1, 3, or 10 mg/kg/day PFHxS were administered by gavage in an aqueous vehicle. Male rats were dosed beginning 14 days before cohabitation and continued until 1 day before sacrifice (a minimum of 42 days). Females were dosed beginning 14 days before cohabitation and continued until 1 day before sacrifice on PND 21 or GD 25 (rats that did not deliver a litter). Endpoints evaluated included: body weight, food consumption, estrous cycling, functional observational battery (FOB; tests of autonomic function, reactivity and sensitivity, excitability, gait and sensorimotor coordination, grip strength, and clinical signs), hematology and clinical chemistry, gross necropsy, organ weights, histopathology, and sperm evaluations. At parturition, litters were evaluated for size and viability; weight of the pups was also recorded. Pups were sacrificed on PND 22.

The following are findings for male F0 rats. Treatment with PFHxS did not affect survival and did not induce clinical signs that could be attributed to the chemical. Terminal body weight in the 10 mg/kg/day groups was approximately 6% lower than controls. Food consumption was not affected. Necropsy did not reveal any treatment-related changes. Histopathological effects were restricted to the liver and

thyroid of males treated with 3 and 10 mg/kg/day. Liver effects consisted of minimal to moderate hypertrophy of centrilobular hepatocytes. The affected hepatocytes were enlarged with an increased amount of dense eosinophilic granular cytoplasm. In the thyroid, the changes consisted of hypertrophy and/or hyperplasia of follicular cells. These effects could have been associated with the liver effects.

Significant organ weight changes consisted of increased absolute and relative liver weight at 3 and 10 mg/kg/day and decreased heart/brain weight at 10 mg/kg/day. Significant hematology changes consisted of decreased hemoglobin at 1 mg/kg/day, decreased red cell count and hematocrit at 3 mg/kg/day, and increased prothrombin time at 0.3 mg/kg/day. Increases in albumin, BUN, alkaline phosphatase, calcium, and albumin/globulin ratio were seen at 10 mg/kg/day. The investigators noted that the alterations in prothrombin time were slight and did not follow a specific trend and the values were within the normal range. There were no significant effects on the FOB or on motor activity and no significant effects on sperm parameters. There were no significant effects in any parameter monitored in F0 females or in pups. Treatment with PFHxS had no significant effect on the gross or microscopic morphology of the spleen, thymus, or lymph nodes. There were no significant effects on sex organ weights or gross or microscopic lesions in the reproductive organs of males and females. Fertility was not affected by treatment with PFHxS and there were no significant effects on sperm parameters. Estrous cycling was not affected by dosing with PFHxS. Treatment with PFHxS did not significantly affect any of the developmental parameters evaluated including gestation length, number of dams delivering litters, averages for implantation sites per delivered litter, number of dams with stillborn pups, number of dams with no live pups, dams with all pups dying, number of pups surviving per litter, sex ratios, litter size, or pup weight. Also, necropsy of the pups showed no treatment-related effects, and pup liver weight was not affected. Treatment with PFHxS had no significant effect on the FOB or motor activity. The battery tested autonomic functions, reactivity and sensitivity to stimuli, excitability, gait and sensorimotor coordination, limb grip strength, and abnormal clinical signs.

***Strengths and Weaknesses:*** The Butenhoff et al. (2009a) study is a well-designed study evaluating male and female reproductive endpoints and developmental endpoints. An adequate number of animals were exposed to three PFHxS dose levels. An additional strength of the study is the inclusion of parameters that evaluated potential neurobehavioral effects, hematological and clinical chemistry parameters, and histopathological examination of the liver and thyroid. Measurement of serum PFHxS levels allowed for estimation of a TWA serum concentration that could be used to calculate a HED. One weakness of the study is that thyroid hormone levels were not measured; these data could have been useful in evaluating the observed histological alterations in the thyroid gland.

***Selection of the Point of Departure for the MRL:*** The HED of the NOAEL of 1 mg/kg/day identified in the Butenhoff et al. (2009a) developmental toxicity study was selected as the POD for the MRL. A TWA serum PFHxS concentration of 73.22 µg/mL was estimated for the adult males exposed to 1 mg/kg/day (Butenhoff et al. 2009a).

***Human Equivalent Dose:*** The HED was calculated based on the assumption that humans would have similar effects as the laboratory animal at a given serum concentration. HEDs that would result in steady-state serum concentrations of PFHxS equal to the estimated TWA serum concentration selected as the POD were calculated using the first-order single-compartment model (see MRL approach section for details). The HED was calculated using Equation A-6 where $C_{ss}$ is 73.22 µg/mL, $K_e=2.23x10^{-4}$; $V_d=0.287$, and AF=1. The $NOAEL_{HED}$ is 0.0047 mg/kg/day

***Uncertainty Factor and Modifying Factor:*** The $NOAEL_{HED}$ is divided by a total uncertainty factor (UF) of 30 and a modifying factor (MF) of 10:

- 3 UF for extrapolation from animals to humans with dosimetric adjustment
- 10 UF for human variability

- 10 MF for database limitations to account for small number of studies examining the toxicity of PFHxS following intermediate-duration exposure and the limited scope of these studies in particular studies examining immunotoxicity, a sensitive endpoint for other perfluoroalkyls.

  $MRL = NOAEL_{HED} \div (UFs \times MF)$
  $0.0047 \text{ mg/kg/day} \div ((10 \times 3) \times 10) = 2x10^{-5} \text{ mg/kg/day}$

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** A discussion of the findings from epidemiological studies is presented in the MRL introduction section. An empirical steady state model was used to estimate the HED from a POD based on a 42-day exposure of adult rats. The resulting HED is lower than the daily 42-day human dose that would be expected to achieve the POD serum concentration.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexane sulfonic acid (PFHxS)
***CAS Numbers:*** 355-46-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** No chronic duration studies were identified for PFHxS. Although adequate data are available for intermediate-duration exposure, ATSDR does not extrapolate across exposure duration.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFHxS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorononanoic acid (PFNA)
***CAS Numbers:*** 375-95-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFNA.

***Rationale for Not Deriving an MRL:*** The only available inhalation exposure study for PFNA (Kinney et al. 1989) was not considered suitable for derivation of an inhalation MRL due to its lack of histopathological examination and short exposure duration.

In the only available inhalation exposure study for PFNA, Kinney et al. (1989) noted labored breathing in rats during and after a 4-hour nose-only exposure to 590 $mg/m^3$ exposure; the study also reported an increase in relative liver weight 5 days after exposure to $\geq$67 $mg/m^3$.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorononanoic acid (PFNA)
***CAS Numbers:*** 375-95-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFNA.

***Rationale for Not Deriving an MRL:*** No intermediate-duration inhalation studies in laboratory animals were identified for PFNA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorononanoic acid (PFNA)
***CAS Numbers:*** 375-95-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFNA.

***Rationale for Not Deriving an MRL:*** No chronic-duration inhalation studies in laboratory animals were identified for PFNA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorononanoic acid (PFNA)
***CAS Numbers:*** 375-95-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFNA.

***Rationale for Not Deriving an MRL:*** An acute-duration oral MRL cannot be derived for PFNA because the study identifying the lowest dose for a non-hepatic effect (Fang et al. 2009) did not measure serum PFNA levels, which are needed for estimating an HED.

A number of studies examined the toxicity of PFNA in rats and mice exposed for acute durations. These studies reported immune, liver, and body weight effects. Immune effects included increases in thymus weight in rats at 1 mg/kg/day (Fang et al. 2009), decreases in thymus and spleen weights in rats at 3 mg/kg/day (Fang et al. 2009, 2010), and an alteration in splenic lymphocyte phenotypes in mice at 1 mg/kg/day (Fang et al. 2008). In the only study examining immune function, no alterations in splenic lymphocyte response to ConA were observed at doses as high as 5 mg/kg/day in mice (Fang et al. 2008). Liver effects included increases in hepatic lipid levels at ≥0.2 mg/kg/day (Wang et al. 2015a), increases in liver weights at ≥0.2 mg/kg/day (Wang et al. 2015a; Kennedy 1987), serum lipid levels at ≥1 mg/kg/day (Fang et al. 2012a, 2012b), hepatocellular vacuolation at 5 mg/kg/day (Fang et al. 2012b), and increases in serum aminotransferases at 5 mg/kg/day (Wang et al. 2015a). Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight and hepatic lipid levels and alterations in serum lipid levels observed in rats and mice, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs.

Decreases in body weight were observed in rats and mice administered 5 mg/kg/day (Hadrup et al. 2016; Wang et al. 2015a).

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorononanoic acid (PFNA)
***CAS Numbers:*** 375-95-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate
***MRL:*** $3x10^{-6}$ mg/kg/day
***Critical Effect:*** Decreased body weight and developmental delays
***Reference:*** Das et al. 2015
***Point of Departure:*** 0.001 mg/kg/day
***Uncertainty Factor:*** 30
***Modifying Factor:*** 10
***LSE Graph Key:*** 39
***Species:*** Mouse

***MRL Summary:*** An intermediate-duration oral MRL of $3x10^{-6}$ mg/kg/day was derived for PFNA based on decreased body weight gain and developmental delays in the offspring of mice administered via gavage PFNA on GDs 1–17 (Das et al. 2015). The MRL is based on a HED NOAEL of 0.001 mg/kg/day and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability), and a modifying factor of 10 for database limitations.

***Selection of the Critical Effect:*** The intermediate-duration database consists of three developmental toxicity studies in rats and mice and a 90-day study in mice. The lowest LOAEL for developmental toxicity was 1.1 mg/kg/day in mice administered PFNA on GDs 1–18; at this dose, decreases in litter size and pup survival were observed (Wolf et al. 2010). At higher doses (2–5 mg/kg/day), decreases in pup body weight, delays in postnatal development (Das et al. 2015; Rogers et al. 2014; Wolf et al. 2010), increases in pup systolic blood pressure (Rogers et al. 2014), and reduced nephron endowment (Rogers et al. 2014) were observed. A study of PPARα knockout mice did not find alterations pup body weight or postnatal development at 2 mg/kg/day (Wolf et al. 2010). In the 90-day study, decreased sperm motility, viability, and number; degenerative changes in seminiferous tubules; and decreased litter size (males mated to unexposed females) were observed at 0.5 mg/kg/day; no changes were observed at 0.2 mg/kg/day (Singh and Singh 2018). A summary of the observed effects is presented in Table A-18.

**Table A-18. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure to PFNA**

| Species and exposure duration | Dose (mg/kg/day) | Effect | Reference |
|---|---|---|---|
| Parkes mouse 90 days | 0.2 | No effects reported | Singh and Singh 2018 |
| | 0.5 | Decreased sperm motility, viability, and number; degenerative changes in seminiferous tubules; decreased litter size | |

**Table A-18. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure to PFNA**

| Species and exposure duration | Dose (mg/kg/day) | Effect | Reference |
|---|---|---|---|
| 129S1/svlm mouse GDs 1–18 (offspring followed until PND 21) | 0.83 | No effects reported | Wolf et al. 2010 |
| | 1.1 | Decreased litter size and pup survival | |
| | 1.5 | No effects reported | |
| | 2.0 | Decreased number of live pups per litter and decreased pup body weight gain | |
| CD-1 mouse GDs 1–17 (offspring followed until PND 287) | 1 | No effects reported | Das et al. 2015 |
| | 3 | Decreased body weight gain and delayed eye opening, preputial separation, and vaginal opening | |
| | 5 | Decreased postnatal survival, 80% mortality between PND 2 and 10 | |
| | 10 | Full litter resorption | |
| Sprague-Dawley rat GDs 1–20 offspring followed through PND 434) | 5 | Decreased birth weight, increased blood pressure at 10 weeks of age; reduced nephron endowment | Rogers et al. 2014 |

GD = gestation day; PFNA = perfluorononanoic acid; PND = postnatal day

***Selection of the Principal Study:*** The lowest LOAEL was 0.5 mg/kg/day identified in the Singh and Singh (2018) reproductive toxicity study. However, this study could not be used to derive an MRL for PFNA because the investigators did not measure serum PFNA levels. Developmental toxicity, including decreases in pup survival, developmental delays, and decreases in birth weight have been observed in three studies. A comparison of the estimated TWA serum PFNA levels (Table A-19) for the Wolf et al. (2010) and Das et al. (2015) studies (measured serum levels were not available from the Rogers et al. 2014 study) showed that the lowest LOAEL for developmental effects was 10.9 µg/mL (Das et al. 2015); this study reported a NOAEL of 6.8 µg/mL. Thus, the Das et al. (2015) study was selected as the principal study for the MRL.

**Table A-19. Summary of Estimated TWA Serum PFNA levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Estimated TWA serum PFNA (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| Parkes mouse 90 days | 0.2 | Not calculated | No effects reported | Singh and Singh 2018 |
| | 0.5 | | Decreased sperm motility, viability, and number; degenerative changes in seminiferous tubules; decreased litter size | |

**Table A-19. Summary of Estimated TWA Serum PFNA levels in Laboratory Animals Following Intermediate-Duration Oral Exposure**

| Species and exposure duration | Dose (mg/kg/day) | Estimated TWA serum PFNA (µg/mL) | Effect | Reference |
|---|---|---|---|---|
| 129S1/svlm mouse GDs 1–18 (offspring followed until PND 21) | 0.83 | 4.47 | No effects reported | Wolf et al. 2010 |
| | 1.1 | 11.6 | Decreased litter size and pup survival | |
| | 1.5 | 10.5 | No effects reported | |
| | 2.0 | 17.6 | Decreased number of live pups per litter and decreased pup body weight gain | |
| CD-1 mouse GDs 1–17 (offspring followed until PND 287 | 1 | 6.8 | No effects reported | Das et al. 2015 |
| | 3 | 10.9 | Decreased body weight gain and delayed eye opening, preputial separation, and vaginal opening | |
| | 5 | 39.7 | Decreased postnatal survival, 80% mortality between PND 2 and 10 | |
| | 10 | NA | Full litter resorption | |
| Sprague-Dawley rat GDs 1–20 (offspring followed through PND 434) | 5 | Not calculated | Decreased birth weight, increased blood pressure at 10 weeks of age; reduced nephron endowment | Rogers et al. 2014 |

GD = gestation day; PFNA perfluorononanoic acid; PND = postnatal day

***Summary of the Principal Study:***

Das KP, Grey BE, Rosen MB, et al. 2015. Developmental toxicity of perfluorononanoic acid in mice. Reprod Toxicol 51:133-144.

Groups of 8–10 timed-pregnant female CD-1 mice were administered via gavage 0, 1, 3, 5, or 10 mg/kg/day PNFA at a dosing volume of 10 ml/kg body weight in deionized water on GDs 1–17. On GD 17, selected mice from each group were sacrificed for maternal and fetal examination, while the remaining mice were allowed to give birth. Pups were observed for postnatal survival up to PND 24 as well as growth and development up to PND 287. The following parameters were used to assess toxicity: clinical observations, maternal body weight, pup body weight (pre- and postnatal), organ weights (liver, gravid uterus weight), number of implantation sites, percent of live fetuses, percent of prenatal loss per litter, and morphological changes (eye opening, vaginal opening, preputial separation).

Maternal weight loss beginning on GD 8 was observed at 10 mg/kg/day; on GD 13, the 10 mg/kg/day group weighed approximately 30% less than controls. The 10 mg/kg/day group was terminated on GD 13. Significant increases in full litter resorptions occurred at 10 mg/kg/day (7/7 compared to 2/8 in controls). There were no adverse effects on pregnancy outcome following *in utero* exposure to 5 mg/kg. Statistically significant dose-related increases in absolute and relative liver weights were observed in dams in the 1, 3, and 5 mg/kg/day groups examined on GD 17, as well as in dams examined on post-weaning day 28. There were no effects on the number of implants, number of live fetuses, or fetal body weight. Relative and absolute fetal liver weight were significantly increased; however, the increase did not appear to be dose-related. Visceral and skeletal examination of fetuses revealed no treatment-related

effects. Increases in postnatal deaths were observed in the 5 mg/kg/day offspring between PND 2 and 10; postnatal survival was approximately 20% on PND 10. Weight gain was significantly reduced in pups from the 3 and 5 mg/kg dose groups from PND 1 to 24. The changes in males were dose-related and persisted from PND 25 to 287. Weight reduction in females was less substantial in comparison with males and returned to control levels by 7 weeks of age. Relative pup liver weights were significantly increased at all doses up to PND 24 and at 3 and 5 mg/kg/day on PND 42. No significant effects on liver weight were detectable by PND 70. Postnatal development (eye opening, preputial separation, and vaginal opening) was significantly delayed (by 2–7 days) at 3 and 5 mg/kg/day.

The serum PFNA levels (means±standard error of the mean) in the pregnant dams (measured at term) were 0.015±0.003, 13.67±1.45, 21.85±3.17, and 79.48±22.69 µg/mL in the 0. 1, 3, and 5 mg/kg/day groups (serum concentrations were provided to ATSDR by C. Lau).

***Strengths and Weaknesses:*** Das et al. (2015) is a well-designed developmental toxicity study in mice. One strength of the study is that it included evaluation of potential anomalies in fetuses, as well as monitoring postnatal growth and development through PND 70. An additional strength of the study is the inclusion of serum and liver PFNA measurements, which allow for cross-species evaluations. Inclusion of measurement of the expression of genes related to PPARα, CAR, and PXR provides valuable mechanisms-of-action data. Although the study tested four PFNA dose levels, increases in maternal morbidity at 10 mg/kg/day and pup lethality at 5 mg/kg/day limited the data available to establish dose-response relationships.

***Selection of the Point of Departure for the MRL:*** The HED of the NOAEL of 1 mg/kg/day identified in the Das et al. (2015) developmental toxicity study was selected as the POD for the MRL. A TWA serum PFNA concentration was estimated for dams using the serum concentration in the control group (0.015 µg/mL) as the baseline concentrations and the terminal concentration for the 1 mg/kg/day group (13.67 µg/mL) resulting in an estimated TWA serum concentration of 6.8 µg/mL.

***Human Equivalent Dose:*** The HED was calculated based on the assumption that humans would have similar effects as the laboratory animal at a given serum concentration. HEDs that would result in steady-state serum concentrations of PFNA equal to the estimated TWA serum concentration selected as the POD were calculated using the first-order single-compartment model (see MRL approach section for details). The HED was calculated using Equation A-6 where $C_{ss}$ is 6.8 µg/mL, $K_e=7.59x10^{-4}$; $V_d=0.2$, and AF=1. The $K_e$ was calculated using the 2.5-year elimination half-life in young women; this value was selected over the 4.3-year value for the combined group of males and older females because the MRL is based on a developmental toxicity study. The $NOAEL_{HED}$ is 0.001 mg/kg/day.

***Uncertainty Factor and Modifying Factor:*** The $NOAEL_{HED}$ is divided by a total uncertainty factor (UF) of 30 and modifying factor (MF) of 10:

- 3 UF for extrapolation from animals to humans with dosimetric adjustment
- 10 UF for human variability
- 10 MF for database limitations to account for small number of studies examining the toxicity of PFNA following intermediate-duration exposure and the limited scope of these studies. The available data suggest that reproductive toxicity may be a more sensitive endpoint than developmental toxicity; however, this endpoint could not be used to derive the MRL because the Singh and Singh (2018) study did not measure serum PFNA levels. Additionally, intermediate-duration studies for other perfluoroalkyls suggest that immune function is a sensitive target of toxicity; however, this potential endpoint has not been examined in intermediate-duration PFNA studies.

$$MRL = NOAEL_{HED} \div (UFs \times MF)$$

0.001 mg/kg/day ÷ ((10 x 3) x 10) = $3x10^{-6}$ mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** A discussion of the findings from epidemiological studies is presented in the MRL introduction section.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorononanoic acid (PFNA)
***CAS Numbers:*** 375-95-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** No chronic-duration studies were identified for PFNA. Although adequate data are available for intermediate-duration exposure, ATSDR does not extrapolate across exposure duration.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFNA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorodecanoic acid (PFDA)
***CAS Numbers:*** 335-76-2
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFDA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorodecanoic acid (PFDA)
***CAS Numbers:*** 335-76-2
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFDA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorodecanoic acid (PFDA)
***CAS Numbers:*** 335-76-2
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFDA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorodecanoic acid (PFDA)
***CAS Numbers:*** 335-76-2
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFDA.

***Rationale for Not Deriving an MRL:*** The available acute oral database for PFDA was not considered adequate for derivation of an MRL because the study identifying the lowest adverse effect level did not measure serum PFDA levels, which are needed to estimate HEDs.

Several laboratory animal studies have examined the acute oral toxicity of PFDA; most were limited in scope. The lowest LOAEL was 1 mg/kg/day for decreases in fetal weight in mice administered PFDA on GDs 6–15 (Harris and Birnbaum 1989). At 12.8 mg/kg/day, decreases in the number of live fetuses per litter were observed; maternal weight loss was also observed at this dose level (Harris and Birnbaum 1989). Another developmental toxicity study did not report alterations in performance on neurobehavioral tests in 2–4-month-old mice administered 10.8 mg/kg/day PFDA on PND 10 (Johansson et al. 2008). Other effects observed in acute exposure studies include decreases in maternal weight gain at 6.4 mg/kg/day (Harris and Birnbaum 1989), weight loss at ≥9.5 mg/kg/day in rats (Kawashima et al. 1995) and mice (Harris and Birnbaum 1989; Permadi et al. 1992, 1993), increases in T3 and T4 levels in mice at 80 mg/kg/day (Harris et al. 1989), decreases in spleen weight in mice at 80 mg/kg/day (Harris et al. 1989), and atrophy and lymphoid depletion in thymus and spleen in mice at 160 mg/kg/day (Harris et al. 1989). Liver effects included increases in liver weight at ≥2.4 mg/kg/day (Brewster and Birnbaum 1989; Harris et al. 1989; Kawashima et al. 1995; Permadi et al. 1992, 1993), increases in hepatic lipid levels at ≥9.5 mg/kg/day (Brewster and Birnbaum 1989; Kawashima et al. 1995), and hepatocellular hypertrophy at ≥20 mg/kg/day (Harris et al. 1989). Although there is uncertainty regarding the exact, and possibly multiple, mechanism(s) for these liver effects, peroxisome proliferation is a likely contributor, a mechanism that cannot be reliably extrapolated to humans (Hall et al. 2012). Therefore, increases in liver weight and hepatic lipid levels and alterations in serum lipid levels observed in rats and mice, in the absence of other degenerative lesions, were not considered appropriate endpoints for deriving MRLs.

To derive MRLs for perfluoroalkyls, ATSDR used the approach of predicting TWA serum perfluoroalkyl levels in laboratory animals or measured serum perfluoroalkyl levels and calculating HEDs for these serum concentrations. For PFOA and PFOS, the Wambaugh et al. (2013) pharmacokinetic model was utilized for predicting the TWA serum perfluoroalkyl concentrations. However, strain-, sex-, and compound-specific model parameters are not available for other perfluoroalkyls. The Harris and Birnbaum (1989) study, which identified the lowest adverse effect level, did not measure maternal serum PFDA levels. Thus, HEDs could not be calculated using animal serum PFDA levels. Other approaches such as “read across” or equivalency factors were considered; however, there are limited data available that would allow for comparison of the toxicity and toxicokinetic properties of different perfluoroalkyls. Peters and Gonzalez (2011) noted that the toxic equivalency factor approach would not be suitable for perfluoroalkyls because the current data suggest that the toxicity of these compounds appear to be mediated by multiple receptors, including PPARα, CAR, and PXR, and that there may be species differences in the response mediated by different receptors. Additionally, available data suggest that there are qualitative differences in the toxicities of various perfluoroalkyls.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorodecanoic acid (PFDA)
***CAS Numbers:*** 335-76-2
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFDA.

***Rationale for Not Deriving an MRL:*** Two studies conducted by Frawley et al. (2018) evaluated the intermediate-duration toxicity of PFDA. In a 28-day study in rats, increases in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration and decreases in phagocytosis by fixed tissue macrophages in the liver were observed in female rats administered 0.25 mg/kg/day PFDA. At 0.5 mg/kg/day, single cell necrosis was observed. In the second study, decreases in splenic T-cells and macrophages were observed in mice administered 1.25 mg/kg PFDA once a week for 4 weeks.

The Frawley et al. (2018) study was not considered for the principal study since it did not measure serum PFDA levels.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorodecanoic acid (PFDA)
***CAS Numbers:*** 335-76-2
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFDA.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroundecanoic acid (PFUnA)
***CAS Numbers:*** 2058-94-8
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFUnA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFUnA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroundecanoic acid (PFUnA)
***CAS Numbers:*** 2058-94-8
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFUnA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFUnA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroundecanoic acid (PFUnA)
***CAS Numbers:*** 2058-94-8
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFUnA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFUnA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroundecanoic acid (PFUnA)
***CAS Numbers:*** 2058-94-8
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFUnA.

***Rationale for Not Deriving an MRL:*** No acute-duration oral studies in laboratory animals were identified for PFUnA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroundecanoic acid (PFUnA)
***CAS Numbers:*** 2058-94-8
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFUnA.

***Rationale for Not Deriving an MRL:*** Intermediate-duration oral database was considered inadequate for derivation of an MRL for PFUnA because the only available study did not measure serum PFUnA levels, which are needed to calculated HEDs (see MRL approach in Appendix A introduction).

One study was identified that examined the oral toxicity of PFUnA in laboratory animals. In this study, decreases in body weight, hematological alterations, increases in liver weight, and centrilobular hypertrophy were observed in rat dams administered 1.0 mg/kg/day for 41–46 days (Takahashi et al. 2014). The study also found decreases in pup body weight on PNDs 0 and 4 at 1.0 mg/kg/day.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroundecanoic acid (PFUnA)
***CAS Numbers:*** 2058-94-8
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFUnA.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFUnA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroheptanoic acid (PFHpA)
***CAS Numbers:*** 375-85-9
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFHpA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFHpA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroheptanoic acid (PFHpA)
***CAS Numbers:*** 375-85-9
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFHpA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFHpA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroheptanoic acid (PFHpA)
***CAS Numbers:*** 375-85-9
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFHpA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFHpA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroheptanoic acid (PFHpA)
***CAS Numbers:*** 375-85-9
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFHpA.

***Rationale for Not Deriving an MRL:*** No oral studies in laboratory animals were identified for PFHpA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroheptanoic acid (PFHpA)
***CAS Numbers:*** 375-85-9
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFHpA.

***Rationale for Not Deriving an MRL:*** No oral studies in laboratory animals were identified for PFHpA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluoroheptanoic acid (PFHpA)
***CAS Numbers:*** 375-85-9
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFHpA.

***Rationale for Not Deriving an MRL:*** No oral studies in laboratory animals were identified for PFHpA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutane sulfonic acid (PFBS)
***CAS Numbers:*** 375-73-5
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFBS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFBS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutane sulfonic acid (PFBS)
***CAS Numbers:*** 375-73-5
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFBS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFBS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutane sulfonic acid (PFBS)
***CAS Numbers:*** 375-73-5
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFBS.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFBS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutane sulfonic acid (PFBS)
***CAS Numbers:*** 375-73-5
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFBS.

***Rationale for Not Deriving an MRL:*** No acute-duration oral studies in laboratory animals were identified for PFBS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutane sulfonic acid (PFBS)
***CAS Numbers:*** 375-73-5
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFBS.

***Rationale for Not Deriving an MRL:*** Several studies have evaluated the toxicity of PFBS following intermediate-duration oral exposure and have identified several targets of toxicity. However, none of these studies included measurement of serum PFBS levels that are needed to calculate a HED and MRL derivation.

Limited data available on the toxicity of PFBS in laboratory animals have identified the liver, kidneys, stomach, and hematological systems and the developing organism as targets of toxicity. Decreases in hemoglobin and hematocrit levels were observed in male rats administered 200 mg/kg/day PFBS for 90 days (Lieder et al. 2009a); decreases in erythrocyte levels were observed at 600 mg/kg/day. Administration of 600 mg/kg/day for 90 days also resulted in tubular and ductal papillary epithelial hyperplasia in the kidneys and necrosis and hyperplasia/hyperkeratosis in the forestomach (Lieder et al. 2009a). Effects in the liver consisted of decreases in plasma triglyceride levels in mice exposed to 30 mg/kg/day for 4–6 weeks (Bijland et al. 2011), increases in absolute and relative liver weight in male rats administered 300 mg/kg/day for at least 70 days (Lieder et al. 2009b) or 900 mg/kg/day for 28 days (3M 2001), and hepatocellular hypertrophy in rats administered 1,000 mg/kg/day in a 2-generation study (Lieder et al. 2009b). In general, no biologically relevant alterations in performance on FOB tests or motor activity tests were observed in rats administered 900 mg/kg/day PFBS for 28 days (3M 2001) or 600 mg/kg/day for 90 days (Lieder et al. 2009a).

Decreases in fetal body weight were observed in two studies involving administration of PFBS to rats on GDs 6–20 (York 2002, 2003a); one study reported a LOAEL of 1,000 mg/kg/day (York 2002) and the other a LOAEL of 2,000 mg/kg/day with a NOAEL of 1,000 mg/kg/day (York 2003a). In a developmental toxicity mouse study, decreases in pup body weight, developmental delays (eye opening and vaginal opening), impaired development of the reproductive system (delay in first estrous, decreases in ovarian follicles, decreases in uterine endometrial and myometrial thickness), and decreases in total T4 and T3 and increases in TSH were observed in the offspring of mice administered 200 mg/kg/day PFBS (Feng et al. 2017). Decreases in maternal total T4, free T4, and total T3 and increases in TSH were observed at 200 mg/kg/day.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutane sulfonic acid (PFBS)
***CAS Numbers:*** 375-73-5
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFBS.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFBS.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutanoic acid (PFBA)
***CAS Numbers:*** 375-22-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFBA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFBA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutanoic acid (PFBA)
***CAS Numbers:*** 375-22-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFBA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFBA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutanoic acid (PFBA)
***CAS Numbers:*** 375-22-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFBA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFBA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutanoic acid (PFBA)
***CAS Numbers:*** 375-22-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFBA.

***Rationale for Not Deriving an MRL:*** Laboratory animal studies for other perfluoroalkyls have identified immunotoxicity and developmental toxicity as sensitive endpoints following acute-duration oral exposure; these potential targets have not been investigated for PFBA. Thus, the database was considered inadequate for identifying a critical endpoint and evaluating dose-response relationships.

Three studies have examined the acute toxicity of PFBA in laboratory animals for a limited number of potential endpoints. Ikeda et al. (1985) reported that administration of approximately 20 mg/kg/day PFBA in the diet to male rats for 2 weeks did not significantly affect relative liver weight, but increased catalase activity in liver homogenates by 42% and induced peroxisome proliferation, as assessed by electron microscopy. In a similar study, dietary administration of approximately 78 mg/kg/day PFBA to male mice for 10 days induced a 63% increase in absolute liver weight (Permadi et al. 1992). The increase in liver weight was accompanied by changes in enzymes involved in drug metabolism and/or in deactivation of reactive oxygen species; however, PFBA did not have a significant effect on parameters of peroxisomal fatty acid β-oxidation (Permadi et al. 1993). In a more comprehensive study, no significant effect on a wide range of endpoints including body and organ weights, hematology and clinical chemistry, and histopathology were observed in rats administered 184 mg/kg/day for 5 days (3M 2007a).

***Agency Contacts (Chemical Managers):*** Melanie Buser

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutanoic acid (PFBA)
***CAS Numbers:*** 375-22-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFBA.

***Rationale for Not Deriving an MRL:*** The available intermediate-duration database was not considered adequate for derivation of an MRL. Although the available studies have examined potentially sensitive endpoints and developmental toxicity and both studies measured serum PFBA levels, the database is missing a reliable estimate of elimination half-life in humans. Chang et al. (2008b) reported serum half-lives in small groups of subjects (<10 subjects); only 2 of the subjects were females. Because developmental toxicity is one of the more sensitive endpoints, data from females is needed in order to estimate the HED.

The intermediate-duration oral database for PFBA consists of a developmental study in mice (Das et al. 2008) and 28- and 90-day gavage studies in rats (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). In the developmental study, PFBA administered to pregnant mice on GDs 1–17 did not affect newborn weight gain or viability (Das et al. 2008). The most sensitive response was a delay in eye opening in the pups at maternal doses of PFBA of 35 mg/kg/day. In the 28- and 90-day studies, hyperplasia/hypertrophy of the follicular epithelium of the thyroid and hepatocellular hypertrophy were observed at ≥30 mg/kg/day (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). In addition, the 90-day study reported hematological alterations in male rats dosed with 30 mg/kg/day PFBA. The NOAEL for these effects was 6 mg/kg/day.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorobutanoic acid (PFBA)
***CAS Numbers:*** 375-22-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFBA.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFBA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorododecanoic acid (PFDoDA)
***CAS Numbers:*** 307-55-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFDoDA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFDoDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorododecanoic acid (PFDoDA)
***CAS Numbers:*** 307-55-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFDoDA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFDoDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorododecanoic acid (PFDoDA)
***CAS Numbers:*** 307-55-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFDoDA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for PFDoDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorododecanoic acid (PFDoDA)
***CAS Numbers:*** 307-55-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFDoDA.

***Rationale for Not Deriving an MRL:*** The database was considered inadequate for derivation of an MRL.

Two studies have examined the acute-oral toxicity of PFDoDA. Shi et al. (2007) reported decreases in body weight and decreases in serum testosterone and estradiol levels in rats following a 14-day gavage administration of 5 mg/kg/day (Shi et al. 2007). The study also reported an increase in serum cholesterol levels at 10 mg/kg/day. In the second study, Zhang et al. (2008) found increases in liver weight and hepatic triglyceride and cholesterol levels in rats administered via gavage ≥5 mg/kg/day for 14 days; these liver effects were not considered relevant to humans. Given the limited number of endpoints examined in Shi et al. (2007) this study, including the lack of histopathological examination, this study was not considered suitable for the derivation of an MRL.

***Agency Contacts (Chemical Managers):*** Melanie Buser

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorododecanoic acid (PFDoDA)
***CAS Numbers:*** 307-55-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFDoDA.

***Rationale for Not Deriving an MRL:*** Three intermediate-duration studies examined the oral toxicity of PFDoDA. Decreases in serum estradiol and increases in serum cholesterol were observed in pubertal females exposed to 3 mg/kg/day PFDoDA on PNDs 24–72 (Shi et al. 2009b). In a second study by this group, decreases in serum testosterone levels were observed in male rats administered 0.2 mg/kg/day PFDoDA for 110 days (Shi et al. 2009a). In a one-generation reproductive/developmental toxicity study, increases in maternal deaths were observed in rats administered 2.5 mg/kg/day PFDoDA prior to mating and throughout gestation, and lactation days 1–5 (Kato et al. 2015). Other effects observed in the male and female parental animals administered 2.5 mg/kg/day included decreases in body weight, decreases in mean corpuscular volume and reticulocytes, single cell hepatocellular necrosis (females only), pancreatic interstitial edema (females only), atrophy of the thymic cortex (females only), atrophy of the adrenal cortex (males only), decrease forelimb grip strength (males only), hemorrhage at the implantation site, and continuous diestrus in unmated females (Kato et al. 2015). The study also reported decreases in pup body weight in the only litter with live pups.

The Shi et al. (2009a) study identified the lowest LOAEL of 0.5 mg/kg/day. However, this study was not considered suitable for MRL derivation because it examined a limited number of endpoints (body weight and reproductive toxicity in males). The Kato et al. (2015) study examined a wide range of endpoints, but effects were only observed at a lethal dose.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorododecanoic acid (PFDoDA)
***CAS Numbers:*** 307-55-1
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFDoDA.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for PFDoDA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanesulfonamide (FOSA)
***CAS Numbers:*** 754-91-6
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for FOSA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for FOSA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanesulfonamide (FOSA)
***CAS Numbers:*** 754-91-6
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for FOSA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for FOSA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanesulfonamide (FOSA)
***CAS Numbers:*** 754-91-6
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for FOSA.

***Rationale for Not Deriving an MRL:*** No inhalation studies in laboratory animals were identified for FOSA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanesulfonamide (FOSA)
***CAS Numbers:*** 754-91-6
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for FOSA.

***Rationale for Not Deriving an MRL:*** The acute-duration database for FOSA was not considered adequate for identifying critical targets of toxicity because the Seacat and Luebker (2000) study only examined a limited number of potential endpoints and the potential developmental and immunological effects (sensitive targets for other perfluoroalkyls) were not examined.

One laboratory animal study evaluated the acute oral toxicity of FOSA. Seacat and Luebker (2000) did not find alterations in body weight or liver weight in rats administered a single dose of 5 mg/kg/day FOSA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanesulfonamide (FOSA)
***CAS Numbers:*** 754-91-6
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for FOSA.

***Rationale for Not Deriving an MRL:*** No intermediate-duration oral studies in laboratory animals were identified for FOSA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorooctanesulfonamide (FOSA)
***CAS Numbers:*** 754-91-6
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for FOSA.

***Rationale for Not Deriving an MRL:*** No chronic-duration oral studies in laboratory animals were identified for FOSA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexanoic acid (PFHxA)
***CAS Numbers:*** 307-24-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration inhalation MRL for PFHxA.

***Rationale for Not Deriving an MRL:*** No acute-duration inhalation studies in laboratory animals were identified for PFHxA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexanoic acid (PFHxA)
***CAS Numbers:*** 307-24-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration inhalation MRL for PFHxA.

***Rationale for Not Deriving an MRL:*** No intermediate-duration inhalation studies in laboratory animals were identified for PFHxA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexanoic acid (PFHxA)
***CAS Numbers:*** 307-24-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL for PFHxA.

***Rationale for Not Deriving an MRL:*** No chronic-duration inhalation studies in laboratory animals were identified for PFHxA.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexanoic acid (PFHxA)
***CAS Numbers:*** 307-24-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** There are insufficient data for derivation of an acute-duration oral MRL for PFHxA.

***Rationale for Not Deriving an MRL:*** The acute database for PFHxA was not considered adequate for derivation of an MRL because serum PFHxA levels at the lowest LOAEL were below the detection limit and an elimination half-life has not been estimated for humans; both of these toxicokinetic parameters are needed to estimate HEDs.

Two developmental toxicity studies conducted by Iwai and Hoberman (2014) examined the acute toxicity of PFHxA following gavage administration. Increases in stillborn pups and decreases in pup body weight were observed at 175 mg/kg/day; no effects were observed at 35 mg/kg/day. In the second study, decreases in birth weight and delayed eye opening was observed at 350 mg/kg/day; the NOAEL was 100 mg/kg/day. These studies were not considered adequate for derivation of an MRL because the measured serum PFHxA levels at 35 and 175 mg/kg/day groups were below the limit of detection. Additionally, the elimination half-life has not been estimated in humans.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexanoic acid (PFHxA)
***CAS Numbers:*** 307-24-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate

***MRL Summary:*** There are insufficient data for derivation of an intermediate-duration oral MRL for PFHxA.

***Rationale for Not Deriving an MRL:*** Five studies have evaluated the intermediate-duration toxicity of PFHxA in rats. A summary of the adverse effects observed in these studies is presented in Table A-20. These studies identify several targets of toxicity including the respiratory tract, erythrocytes, thyroid, thymus, and developing organism; the lowest LOAEL is 100 mg/kg/day for nasal lesions and decrease in body weight gain in males. None of the available studies evaluated immune function, which has been identified as a sensitive target in intermediate oral studies for other perfluoroalkyls.

The data are considered inadequate for MRL derivation because an elimination half-life has not been estimated in humans. Thus, a HED cannot be calculated and an MRL cannot be derived.

**Table A-20. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure to PFHxA**

| Species and exposure duration | Dose (mg/kg/day) | Effect | Reference |
|---|---|---|---|
| Rat<br>92–93 days (GW)<br>30 M, 30 F | 20 | No effects observed | Loveless et al. 2009 |
| | 100 | Degeneration/atrophy of nasal olfactory epithelium | |
| | 500 | Respiratory metaplasia, decreased RBC, hemoglobin, and hematocrit; increased reticulocytes; thyroid follicular epithelial hypertrophy | |
| Rat<br>110–120 days (premating, gestation, lactation) (GW)<br>20 M, 20 F | 20 | No effect observed | Loveless et al. 2009 |
| | 100 | Decreased weight gain in males | |
| | 500 | Decreased maternal weight gain, decreased pup body weight during lactation period | |
| Rat<br>90 days (GW)<br>10 M, 10 F | 10 | No effects observed | Chengelis et al. 2009b |
| | 50 | No effects observed | |
| | 200 | Slight decrease in RBC, hemoglobin, and hematocrit and increase in reticulocytes | |

**Table A-20. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure to PFHxA**

| Species and exposure duration | Dose (mg/kg/day) | Effect | Reference |
|---|---|---|---|
| Rat<br>32–44 days (GW)<br>10–15 M, 10–15 F | 50 | No effects observed | Kirkpatrick 2005 |
| | 150 | Decreased hemoglobin levels (males only) | |
| | 315 (TWA dose) | Decreased hemoglobin levels (males only), increased reticulocyte levels (males only), thymic atrophy (females only) | |
| Rat<br>GDs 1–20 (GW)<br>22 F | 20 | No effect observed | Loveless et al. 2009 |
| | 100 | No effect observed | |
| | 500 | Decreased maternal weight gain; decreased fetal body weight | |

F = female(s); GD = gestation day; (GW) = gavage in water; M = male(s); RBC = red blood cell; TWA = time-weighted average

***Agency Contacts (Chemical Managers):*** Melanie Buser

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Perfluorohexanoic acid (PFHxA)
***CAS Numbers:*** 307-24-4
***Date:*** March 2020
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL for PFHxA.

***Rationale for Not Deriving an MRL:*** The chronic duration oral database for PFHxA is not considered adequate for derivation of a chronic MRL because the only study available did not measure serum PFHxA levels and elimination half-life data are not available for humans. These toxicokinetic data are needed to derive HEDs.

One study has evaluated the chronic oral toxicity of PFHxA in laboratory animals (Klaunig et al. 2015). Exposure to female rats to 200 mg/kg/day resulted in hematological alterations (decreases in red blood cells and hemoglobin levels and increases in reticulocyte counts), renal effects (tubular degeneration, necrosis, increased urine volume and reduced specific gravity), and liver effects (necrosis); no adverse alterations were observed at 30 mg/kg/day or at 100 mg/kg/day in males. This study was not considered suitable for derivation of an MRL because serum PFHxA levels were not measured. Additionally, an elimination half-life has not been estimated in humans.

***Agency Contacts (Chemical Managers):*** Melanie Buser

# APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR PERFLUOROALKYLS

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to perfluoroalkyls.

## B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for perfluoroalkyls. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of perfluoroalkyls have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of perfluoroalkyls are presented in Table B-1.

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

| |
|---|
| Other noncancer effects |
| Cancer |
| Toxicokinetics |
| Absorption |
| Distribution |
| Metabolism |
| Excretion |
| PBPK models |
| Biomarkers |
| Biomarkers of exposure |
| Biomarkers of effect |
| Interactions with other chemicals |
| Potential for human exposure |
| Releases to the environment |
| Air |
| Water |
| Soil |
| Environmental fate |
| Transport and partitioning |
| Transformation and degradation |
| Environmental monitoring |
| Air |
| Water |
| Sediment and soil |
| Other media |
| Biomonitoring |
| General populations |
| Occupation populations |

### B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for perfluoroalkyls released for public comment in 2015. The following main databases were searched in March 2008, September/October 2013, May 2016, and September 2018:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for perfluoroalkyls. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to perfluoroalkyls were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| **PubMed** | |
| 9/11/2018 | ((1763-23-1[rn] OR 2058-94-8[rn] OR 2355-31-9[rn] OR 2991-50-6[rn] OR 307-55-1[rn] OR 335-67-1[rn] OR 335-76-2[rn] OR 355-46-4[rn] OR 375-22-4[rn] OR 375-73-5[rn] OR 375-85-9[rn] OR 375-95-1[rn] OR 754-91-6[rn] OR "perfluorododecanoic acid"[nm] OR "perfluorobutanesulfonic acid"[nm] OR "1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid"[tw] OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid"[tw] OR "1-Perfluorobutanesulfonic acid"[tw] OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid"[tw] OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "C11-PFA"[tw] OR "et-pfosa-acoh"[tw] OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-"[tw] OR "Henicosafluoroundecanoic acid"[tw] OR "heptadecafluoro-1-octane sulfonic acid"[tw] OR "Heptadecafluoro-1-octanesulfonic acid"[tw] OR "heptadecafluorooctane sulfonic acid"[tw] OR "Heptadecafluorooctane-1-sulphonic acid"[tw] OR "Heptadecafluorooctanesulphonamide"[tw] OR "Heptafluoro-1-butanoic acid"[tw] OR "Heptafluorobutanoic acid"[tw] OR "Heptafluorobutyric acid"[tw] OR "me-pfosa-acoh"[tw] OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine"[tw] OR "Ndfda"[tw] OR "Nonadecafluoro-n-decanoic acid"[tw] OR "Nonadecafluorodecanoic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Nonafluorobutanesulfonic acid"[tw] OR "Pentadecafluoro-1-octanoic acid"[tw] OR "Pentadecafluoro-n-octanoic acid"[tw] OR "Pentadecafluorooctanoic acid"[tw] OR "Pentyl perfluorobutanoate"[tw] OR "Perfluoro-n-decanoic acid"[tw] OR "Perfluoro-n-heptanoic acid"[tw] OR "Perfluoro-n-nonanoic acid"[tw] OR "Perfluoro-n-undecanoic acid"[tw] OR "Perfluorobutane sulfonic acid"[tw] OR "Perfluorobutanesulfonic acid"[tw] OR "Perfluorobutanoic acid"[tw] OR "Perfluorobutyric acid"[tw] OR "Perfluorocaprylic acid"[tw] OR "Perfluoroctanoic acid"[tw] OR "Perfluoroctylsulfonamide"[tw] OR "Perfluorodecanoic acid"[tw] OR "Perfluorododecanoic acid"[tw] OR "Perfluorododecanoic acid "[tw] OR "Perfluoroheptanecarboxylic acid"[tw] OR "Perfluoroheptanoic acid"[tw] OR "Perfluorohexane sulfonic acid"[tw] OR "Perfluorohexane-1-sulphonic acid"[tw] OR "perfluorohexanesulfonate"[tw] OR "perfluorohexanesulfonic acid"[tw] OR "Perfluorolauric acid"[tw] OR "Perfluorononan-1-oic acid"[tw] OR "Perfluorononanoic acid"[tw] OR "Perfluorooctane sulfonamide"[tw] OR "Perfluorooctane sulfonate"[tw] OR "Perfluorooctane sulfonic acid "[tw] OR "perfluorooctane sulphonic acid"[tw] OR "Perfluorooctanesulfonamide"[tw] OR "Perfluorooctanesulfonate"[tw] OR "perfluorooctanesulfonic acid"[tw] OR "Perfluorooctanesulfonic acid amide"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctylsulfonic acid"[tw] OR "Perfluoropropanecarboxylic acid"[tw] OR "Perfluoroundecanoic acid"[tw] OR "pfbus"[tw] OR "PFDA"[tw] OR "pfdea"[tw] OR "pfdoa"[tw] OR "Pfhpa"[tw] OR "PFHS cpd"[tw] OR "pfhxs"[tw] OR "pfna"[tw] OR "PFOA"[tw] OR "PFOS"[tw] OR "pfsoa"[tw] OR "Pfua"[tw] OR "Tricosafluorododecanoic acid"[tw] OR "Tridecafluoro-1-heptanoic acid"[tw] OR "Tridecafluoroheptanoic acid"[tw]) AND (2015/05/01:3000[dp] OR 2016/05/01:3000[mhda] OR 2016/05/01:3000[crdat] OR 2016/05/01:3000[edat])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR "pharmacology"[sh:noexp] OR toxicokinetics[mh:noexp] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])))<br><br>(("FC-143 surfactant"[nm] OR 307-24-4[rn] OR 3825-26-1[rn] OR "Hexanoic acid, 2,2,3,3,4,4,5,5,6,6,6-undecafluoro-"[tw] OR "Hexanoic acid, undecafluoro-"[tw] OR "Perfluorohexanoic acid"[tw] OR "Undecafluoro-1-hexanoic acid"[tw] OR "Undecafluorohexanoic acid"[tw] OR "Ammonium pentadecafluorooctanoate"[tw] OR "Ammonium perfluorocaprilate"[tw] OR "Ammonium perfluorocaprylate"[tw] OR "Ammonium perfluorooctanoate"[tw] OR "FC 143"[tw] OR "Octanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-, ammonium salt"[tw] OR "Octanoic acid, pentadecafluoro-, ammonium salt"[tw] OR "Pentadecafluoro-1-octanoic acid, ammonium salt"[tw] OR "Pentadecafluorooctanoic acid, ammonium salt"[tw] OR "Perfluoroammonium octanoate"[tw] OR "Perfluorooctanoic acid, ammonium salt"[tw]) NOT (1763-23-1[rn] OR 2058-94-8[rn] OR 2355-31-9[rn] OR 2991-50-6[rn] OR 307-55-1[rn] OR 335-67-1[rn] OR 335-76-2[rn] OR 355-46-4[rn] OR 375-22-4[rn] OR 375-73-5[rn] OR 375-85-9[rn] OR 375-95-1[rn] OR 754-91-6[rn] OR "perfluorododecanoic acid"[nm] OR "perfluorobutanesulfonic acid"[nm] OR "1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid"[tw] OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid"[tw] OR "1-Perfluorobutanesulfonic acid"[tw] OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid"[tw] OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "C11-PFA"[tw] OR "et-pfosa-acoh"[tw] OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-"[tw] OR "Henicosafluoroundecanoic acid"[tw] OR "heptadecafluoro-1-octane sulfonic acid"[tw] OR "Heptadecafluoro-1-octanesulfonic acid"[tw] OR "heptadecafluorooctane sulfonic acid"[tw] OR "Heptadecafluorooctane-1-sulphonic acid"[tw] OR "Heptadecafluorooctanesulphonamide"[tw] OR "Heptafluoro-1-butanoic acid"[tw] OR "Heptafluorobutanoic acid"[tw] OR "Heptafluorobutyric acid"[tw] OR "me-pfosa-acoh"[tw] OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine"[tw] OR "Ndfda"[tw] OR "Nonadecafluoro-n-decanoic acid"[tw] OR "Nonadecafluorodecanoic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Nonafluorobutanesulfonic acid"[tw] OR "Pentadecafluoro-1-octanoic acid"[tw] OR "Pentadecafluoro-n-octanoic acid"[tw] OR "Pentadecafluorooctanoic acid"[tw] OR "Pentyl perfluorobutanoate"[tw] OR "Perfluoro-n-decanoic acid"[tw] OR "Perfluoro-n-heptanoic acid"[tw] OR "Perfluoro-n-nonanoic acid"[tw] OR "Perfluoro-n-undecanoic acid"[tw] OR "Perfluorobutane sulfonic acid"[tw] OR "Perfluorobutanesulfonic acid"[tw] OR "Perfluorobutanoic acid"[tw] OR "Perfluorobutyric acid"[tw] OR "Perfluorocaprylic acid"[tw] OR "Perfluoroctanoic acid"[tw] OR "Perfluoroctylsulfonamide"[tw] OR "Perfluorodecanoic acid"[tw] OR "Perfluorododecanoic acid"[tw] OR "Perfluorododecanoic acid "[tw] OR "Perfluoroheptanecarboxylic acid"[tw] OR "Perfluoroheptanoic acid"[tw] OR "Perfluorohexane sulfonic acid"[tw] OR "Perfluorohexane-1-sulphonic acid"[tw] OR "perfluorohexanesulfonate"[tw] OR "perfluorohexanesulfonic acid"[tw] OR "Perfluorolauric acid"[tw] OR "Perfluorononan-1-oic acid"[tw] OR "Perfluorononanoic acid"[tw] OR "Perfluorooctane sulfonamide"[tw] OR "Perfluorooctane sulfonate"[tw] OR "Perfluorooctane sulfonic acid "[tw] OR "perfluorooctane sulphonic acid"[tw] OR "Perfluorooctanesulfonamide"[tw] OR "Perfluorooctanesulfonate"[tw] OR "perfluorooctanesulfonic acid"[tw] OR "Perfluorooctanesulfonic acid amide"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctylsulfonic acid"[tw] OR "Perfluoropropanecarboxylic acid"[tw] OR "Perfluoroundecanoic acid"[tw] OR "pfbus"[tw] OR "PFDA"[tw] OR "pfdea"[tw] OR "pfdoa"[tw] OR "Pfhpa"[tw] OR "PFHS cpd"[tw] OR "pfhxs"[tw] OR "pfna"[tw] OR "PFOA"[tw] OR "PFOS"[tw] OR "pfsoa"[tw] OR "Pfua"[tw] OR "Tricosafluorododecanoic acid"[tw] OR "Tridecafluoro-1-heptanoic acid"[tw] OR "Tridecafluoroheptanoic acid"[tw])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR "pharmacology"[sh:noexp] OR toxicokinetics[mh:noexp] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])))) |
| 05/24/2016 | (((((("1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid"[tw] OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid"[tw] OR "1-Perfluorobutanesulfonic acid"[tw] OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid"[tw] OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "C11-PFA"[tw] OR "et-pfosa-acoh"[tw] OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-"[tw] OR "Henicosafluoroundecanoic acid"[tw] OR "heptadecafluoro-1-octane sulfonic acid"[tw] OR "Heptadecafluoro-1-octanesulfonic acid"[tw] OR "heptadecafluorooctane sulfonic acid"[tw] OR "Heptadecafluorooctane-1-sulphonic acid"[tw] OR "Heptadecafluorooctanesulphonamide"[tw] OR "Heptafluoro-1-butanoic acid"[tw] OR "Heptafluorobutanoic acid"[tw] OR "Heptafluorobutyric acid"[tw] OR "me-pfosa-acoh"[tw] OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine"[tw] OR "Ndfda"[tw] OR "Nonadecafluoro-n-decanoic acid"[tw] OR "Nonadecafluorodecanoic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Nonafluorobutanesulfonic acid"[tw] OR "Pentadecafluoro-1-octanoic acid"[tw] OR "Pentadecafluoro-n-octanoic acid"[tw] OR "Pentadecafluorooctanoic acid"[tw] OR "Pentyl perfluorobutanoate"[tw] OR "Perfluoro-n-decanoic acid"[tw] OR "Perfluoro-n-heptanoic acid"[tw] OR "Perfluoro-n-nonanoic acid"[tw] OR "Perfluoro-n-undecanoic acid"[tw] OR "Perfluorobutane sulfonic acid"[tw] OR "Perfluorobutanesulfonic acid"[tw] OR "Perfluorobutanoic acid"[tw] OR "Perfluorobutyric acid"[tw] OR "Perfluorocaprylic acid"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctylsulfonamide"[tw] OR "Perfluorodecanoic acid"[tw] OR "Perfluorododecanoic acid "[tw] OR "Perfluorododecanoic acid"[tw] OR "Perfluoroheptanecarboxylic acid"[tw] OR "Perfluoroheptanoic acid"[tw] OR "Perfluorohexane sulfonic acid"[tw] OR "Perfluorohexane-1-sulphonic acid"[tw] OR "perfluorohexanesulfonate"[tw] OR "perfluorohexanesulfonic acid"[tw] OR "Perfluorolauric acid"[tw] OR "Perfluorononan-1-oic acid"[tw] OR "Perfluorononanoic acid"[tw] OR "Perfluorooctane sulfonamide"[tw] OR "Perfluorooctane sulfonate"[tw] OR "Perfluorooctane sulfonic acid "[tw] OR "perfluorooctane sulphonic acid"[tw] OR "Perfluorooctanesulfonamide"[tw] OR "Perfluorooctanesulfonate"[tw] OR "Perfluorooctanesulfonic acid amide"[tw] OR "perfluorooctanesulfonic acid"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctylsulfonic acid"[tw] OR "Perfluoropropanecarboxylic acid"[tw] OR "Perfluoroundecanoic acid"[tw] OR "pfbus"[tw] OR "PFDA"[tw] OR "pfdea"[tw] OR "pfdoa"[tw] OR "Pfhpa"[tw] OR "PFHS cpd"[tw] OR "pfhxs"[tw] OR "pfna"[tw] OR "PFOA"[tw] OR "PFOS"[tw] OR "pfsoa"[tw] OR "Pfua"[tw] OR "Tricosafluorododecanoic acid"[tw] OR "Tridecafluoro-1-heptanoic acid"[tw] OR "Tridecafluoroheptanoic acid"[tw]) AND (2013/09/01:3000[crdat] OR 2013/09/01:3000[edat])) NOT medline[sb]))))) OR ((((("1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid"[tw] OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid"[tw] OR "1-Perfluorobutanesulfonic acid"[tw] OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid"[tw] OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "C11-PFA"[tw] OR "et-pfosa-acoh"[tw] OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-"[tw] OR "Henicosafluoroundecanoic acid"[tw] OR "heptadecafluoro-1-octane sulfonic acid"[tw] OR "Heptadecafluoro-1-octanesulfonic acid"[tw] OR "heptadecafluorooctane sulfonic acid"[tw] OR "Heptadecafluorooctane-1-sulphonic acid"[tw] OR "Heptadecafluorooctanesulphonamide"[tw] OR "Heptafluoro-1-butanoic acid"[tw] OR "Heptafluorobutanoic acid"[tw] OR "Heptafluorobutyric acid"[tw] OR "me-pfosa-acoh"[tw] OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine"[tw] OR "Ndfda"[tw] OR "Nonadecafluoro-n-decanoic acid"[tw] OR "Nonadecafluorodecanoic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Nonafluorobutanesulfonic acid"[tw] OR "Pentadecafluoro-1-octanoic |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | acid"[tw] OR "Pentadecafluoro-n-octanoic acid"[tw] OR "Pentadecafluorooctanoic acid"[tw] OR "Pentyl perfluorobutanoate"[tw] OR "Perfluoro-n-decanoic acid"[tw] OR "Perfluoro-n-heptanoic acid"[tw] OR "Perfluoro-n-nonanoic acid"[tw] OR "Perfluoro-n-undecanoic acid"[tw] OR "Perfluorobutane sulfonic acid"[tw] OR "Perfluorobutanesulfonic acid"[tw] OR "Perfluorobutanoic acid"[tw] OR "Perfluorobutyric acid"[tw] OR "Perfluorocaprylic acid"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctylsulfonamide"[tw] OR "Perfluorodecanoic acid"[tw] OR "Perfluorododecanoic acid "[tw] OR "Perfluorododecanoic acid"[tw] OR "Perfluoroheptanecarboxylic acid"[tw] OR "Perfluoroheptanoic acid"[tw] OR "Perfluorohexane sulfonic acid"[tw] OR "Perfluorohexane-1-sulphonic acid"[tw] OR "perfluorohexanesulfonate"[tw] OR "perfluorohexanesulfonic acid"[tw] OR "Perfluorolauric acid"[tw] OR "Perfluorononan-1-oic acid"[tw] OR "Perfluorononanoic acid"[tw] OR "Perfluorooctane sulfonamide"[tw] OR "Perfluorooctane sulfonate"[tw] OR "Perfluorooctane sulfonic acid "[tw] OR "perfluorooctane sulphonic acid"[tw] OR "Perfluorooctanesulfonamide"[tw] OR "Perfluorooctanesulfonate"[tw] OR "Perfluorooctanesulfonic acid amide"[tw] OR "perfluorooctanesulfonic acid"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctylsulfonic acid"[tw] OR "Perfluoropropanecarboxylic acid"[tw] OR "Perfluoroundecanoic acid"[tw] OR "pfbus"[tw] OR "PFDA"[tw] OR "pfdea"[tw] OR "pfdoa"[tw] OR "Pfhpa"[tw] OR "PFHS cpd"[tw] OR "pfhxs"[tw] OR "pfna"[tw] OR "PFOA"[tw] OR "PFOS"[tw] OR "pfsoa"[tw] OR "Pfua"[tw] OR "Tricosafluorododecanoic acid"[tw] OR "Tridecafluoro-1-heptanoic acid"[tw] OR "Tridecafluoroheptanoic acid"[tw] OR 1763-23-1[rn] OR 2058-94-8[rn] OR 2355-31-9[rn] OR 2991-50-6[rn] OR 307-55-1[rn] OR 335-67-1[rn] OR 335-76-2[rn] OR 355-46-4[rn] OR 375-22-4[rn] OR 375-73-5[rn] OR 375-85-9[rn] OR 375-95-1[rn] OR 754-91-6[rn]) AND (2013/09/01:3000[mhda] OR 2013/09/01:3000[crdat] OR 2013/09/01:3000[edat])) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])))) |
| 10/03/2013 | ("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR " RNA, Messenger "[mh] OR " RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh]) AND ((335-67-1[rn] OR 1763-23-1[rn] OR 355-46-4[rn] OR 2991-50-6[rn] OR 2355-31-9[rn] OR 335-76-2[rn] OR 375-73-5[rn] OR 375-85-9[rn] OR 375-95-1[rn] OR 754-91-6[rn] OR 2058-94-8[rn] OR 307-55-1[rn] OR 375-22-4[rn] OR 80AM718FML[rn]) AND 2007/05/01:2013/10/03[dp]) |
| 09/19/2013 | (((335-67-1[rn] OR 1763-23-1[rn] OR 355-46-4[rn] OR 2991-50-6[rn] OR 2355-31-9[rn] OR 335-76-2[rn] OR 375-73-5[rn] OR 375-85-9[rn] OR 375-95-1[rn] OR 754-91-6[rn] OR 2058-94-8[rn] OR 307-55-1[rn] OR 375-22-4[rn] OR 80AM718FML[rn]) AND 2007/05/01:2013/09/19[dp]) AND (((Caprylates/metabolism[MeSH Terms] OR Fluorocarbons/metabolism[MeSH Terms] OR "Alkanesulfonic Acids/metabolism"[MeSH Terms] OR "Sulfonic Acids/metabolism"[MeSH Terms] OR "Decanoic Acids/metabolism"[MeSH Terms] OR "Heptanoic Acids/metabolism"[MeSH Terms] OR "Hydrocarbons, Fluorinated/metabolism"[MeSH Terms] OR "Fatty Acids/metabolism"[MeSH Terms] |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | OR Sulfonamides/metabolism[MeSH Terms]) AND ("humans"[MeSH Terms] OR "animals"[MeSH Terms])) OR ((Caprylates[MeSH Terms] OR Fluorocarbons[MeSH Terms] OR "Alkanesulfonic Acids"[MeSH Terms] OR "Sulfonic Acids"[MeSH Terms] OR "Decanoic Acids"[MeSH Terms] OR "Heptanoic Acids"[MeSH Terms] OR "Hydrocarbons, Fluorinated"[MeSH Terms] OR "Fatty Acids"[MeSH Terms] OR Sulfonamides[MeSH Terms]) AND (Endocrine System[mh] OR Hormones[mh] OR Endocrine disruptors[mh])) OR ((Caprylates[MeSH Terms] OR Fluorocarbons[MeSH Terms] OR "Alkanesulfonic Acids"[MeSH Terms] OR "Sulfonic Acids"[MeSH Terms] OR "Decanoic Acids"[MeSH Terms] OR "Heptanoic Acids"[MeSH Terms] OR "Hydrocarbons, Fluorinated"[MeSH Terms] OR "Fatty Acids"[MeSH Terms] OR Sulfonamides[MeSH Terms]) AND "environmental exposure"[MeSH Terms]) OR ((Caprylates[MeSH Terms] OR Fluorocarbons[MeSH Terms] OR "Alkanesulfonic Acids"[MeSH Terms] OR "Sulfonic Acids"[MeSH Terms] OR "Decanoic Acids"[MeSH Terms] OR "Heptanoic Acids"[MeSH Terms] OR "Hydrocarbons, Fluorinated"[MeSH Terms] OR "Fatty Acids"[MeSH Terms] OR Sulfonamides[MeSH Terms]) AND "chemically induced"[MeSH Subheading]) OR ((((((((((("caprylates/adverse effects"[MeSH Terms] OR "caprylates/antagonists and inhibitors"[MeSH Terms] OR "caprylates/blood"[MeSH Terms] OR "caprylates/cerebrospinal fluid"[MeSH Terms] OR "caprylates/pharmacokinetics"[MeSH Terms] OR "caprylates/poisoning"[MeSH Terms] OR "caprylates/toxicity"[MeSH Terms] OR "caprylates/urine"[MeSH Terms])))) OR (("fluorocarbons/adverse effects"[MeSH Terms] OR "fluorocarbons/antagonists and inhibitors"[MeSH Terms] OR "fluorocarbons/blood"[MeSH Terms] OR "fluorocarbons/pharmacokinetics"[MeSH Terms] OR "fluorocarbons/poisoning"[MeSH Terms] OR "fluorocarbons/toxicity"[MeSH Terms] OR "fluorocarbons/urine"[MeSH Terms]))) OR (("alkanesulfonic acids/adverse effects"[MeSH Terms] OR "alkanesulfonic acids/antagonists and inhibitors"[MeSH Terms] OR "alkanesulfonic acids/blood"[MeSH Terms] OR "alkanesulfonic acids/cerebrospinal fluid"[MeSH Terms] OR "alkanesulfonic acids/pharmacokinetics"[MeSH Terms] OR "alkanesulfonic acids/poisoning"[MeSH Terms] OR "alkanesulfonic acids/toxicity"[MeSH Terms] OR "alkanesulfonic acids/urine"[MeSH Terms]))) OR (("sulfonic acids/adverse effects"[MeSH Terms] OR "sulfonic acids/antagonists and inhibitors"[MeSH Terms] OR "sulfonic acids/blood"[MeSH Terms] OR "sulfonic acids/cerebrospinal fluid"[MeSH Terms] OR "sulfonic acids/pharmacokinetics"[MeSH Terms] OR "sulfonic acids/poisoning"[MeSH Terms] OR "sulfonic acids/toxicity"[MeSH Terms] OR "sulfonic acids/urine"[MeSH Terms]))) OR (("decanoic acids/adverse effects"[MeSH Terms] OR "decanoic acids/antagonists and inhibitors"[MeSH Terms] OR "decanoic acids/blood"[MeSH Terms] OR "decanoic acids/pharmacokinetics"[MeSH Terms] OR "decanoic acids/poisoning"[MeSH Terms] OR "decanoic acids/toxicity"[MeSH Terms] OR "decanoic acids/urine"[MeSH Terms]))) OR (("heptanoic acids/adverse effects"[MeSH Terms] OR "heptanoic acids/antagonists and inhibitors"[MeSH Terms] OR "heptanoic acids/blood"[MeSH Terms] OR "heptanoic acids/cerebrospinal fluid"[MeSH Terms] OR "heptanoic acids/pharmacokinetics"[MeSH Terms] OR "heptanoic acids/poisoning"[MeSH Terms] OR "heptanoic acids/toxicity"[MeSH Terms] OR "heptanoic acids/urine"[MeSH Terms]))) OR (("hydrocarbons, fluorinated/adverse effects"[MeSH Terms] OR "hydrocarbons, fluorinated/antagonists and inhibitors"[MeSH Terms] OR "hydrocarbons, fluorinated/blood"[MeSH Terms] OR "hydrocarbons, fluorinated/cerebrospinal fluid"[MeSH Terms] OR "hydrocarbons, fluorinated/pharmacokinetics"[MeSH Terms] OR "hydrocarbons, fluorinated/toxicity"[MeSH Terms] OR "hydrocarbons, fluorinated/urine"[MeSH Terms]))) OR (("fatty acids/adverse effects"[MeSH Terms] OR "fatty acids/antagonists and inhibitors"[MeSH Terms] OR "fatty acids/blood"[MeSH Terms] OR "fatty acids/cerebrospinal fluid"[MeSH Terms] OR "fatty acids/pharmacokinetics"[MeSH Terms] OR "fatty acids/poisoning"[MeSH Terms] OR "fatty acids/toxicity"[MeSH Terms] OR "fatty acids/urine"[MeSH Terms]))) OR (("sulfonamides/adverse effects"[MeSH Terms] OR "sulfonamides/antagonists and inhibitors"[MeSH Terms] OR "sulfonamides/blood"[MeSH Terms] OR "sulfonamides/cerebrospinal fluid"[MeSH Terms] OR "sulfonamides/pharmacokinetics"[MeSH Terms] OR "sulfonamides/poisoning"[MeSH Terms] OR "sulfonamides/toxicity"[MeSH Terms] OR "sulfonamides/urine"[MeSH Terms])))))) OR (("Perfluorooctanoic acid"[tw] OR "Pentadecafluoro-1-octanoic acid"[tw] OR "Pentadecafluoro-n-octanoic acid"[tw] OR "Pentadecafluorooctanoic acid"[tw] OR "Perfluorocaprylic acid"[tw] OR "Perfluoroctanoic acid"[tw] OR "Perfluoroheptanecarboxylic acid"[tw] OR "Perfluorooctanoic acid"[tw] OR "Pentadecafluorooctanoic acid"[tw] OR "Perfluorooctanoic acid"[tw] OR "Perfluorooctane sulfonic acid "[tw] OR "Heptadecafluoro-1-octanesulfonic acid"[tw] OR "heptadecafluoro-1-octane sulfonic acid"[tw] OR "Heptadecafluorooctane-1-sulphonic acid"[tw] OR "heptadecafluorooctane sulfonic |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | acid"[tw] OR "Perfluorooctane sulfonate"[tw] OR "Perfluorooctylsulfonic acid"[tw] OR "perfluorooctane sulphonic acid"[tw] OR "perfluorooctanesulfonic acid"[tw] OR "Perfluorooctanesulfonate"[tw] OR "Heptadecafluorooctane-1-sulphonic acid1-Perfluorooctanesulfonic acid"[tw] OR "Perfluorohexane sulfonic acid"[tw] OR "pfhxs"[tw] OR "perfluorohexanesulfonic acid"[tw] OR "perfluorohexanesulfonate"[tw] OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid"[tw] OR "Perfluorohexane-1-sulphonic acid"[tw] OR "PFHS cpd"[tw] OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "et-pfosa-acoh"[tw] OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine"[tw] OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-"[tw] OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid"[tw] OR "me-pfosa-acoh"[tw] OR "Perfluorodecanoic acid"[tw] OR "Nonadecafluoro-n-decanoic acid"[tw] OR "Nonadecafluorodecanoic acid"[tw] OR "Perfluoro-N-decanoic acid"[tw] OR "Perfluoro-n-decanoic acid"[tw] OR "Perfluorodecanoic acid"[tw] OR "Nonadecafluorodecanoic acid"[tw] OR "Perfluoro-N-decanoic acid"[tw] OR "Perfluorobutane sulfonic acid"[tw] OR "Perfluorobutanesulfonic acid"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid"[tw] OR "1-Perfluorobutanesulfonic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Nonafluorobutanesulfonic acid"[tw] OR "Pentyl perfluorobutanoate"[tw] OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid"[tw] OR "Nonafluoro-1-butanesulfonic acid"[tw] OR "Perfluoroheptanoic acid"[tw] OR "Tridecafluoro-1-heptanoic acid"[tw] OR "Perfluoro-n-heptanoic acid"[tw] OR "Perfluoroheptanoic acid"[tw] OR "Tridecafluoroheptanoic acid"[tw] OR "Perfluorononanoic acid"[tw] OR "Perfluoro-n-nonanoic acid"[tw] OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid"[tw] OR "Perfluorononan-1-oic acid"[tw] OR "Perfluorooctane sulfonamide"[tw] OR "Perfluorooctanesulfonamide"[tw] OR "Perfluoroctylsulfonamide"[tw] OR "Perfluorooctanesulfonic acid amide"[tw] OR "Heptadecafluorooctanesulphonamide"[tw] OR "Perfluoroundecanoic acid"[tw] OR "Perfluoro-n-undecanoic acid"[tw] OR "Henicosafluoroundecanoic acid"[tw] OR "Perfluorododecanoic acid "[tw] OR "Perfluorododecanoic acid"[tw] OR "Tricosafluorododecanoic acid"[tw] OR "Perfluorolauric acid"[tw] OR "Perfluorobutyric acid"[tw] OR "Heptafluorobutyric acid"[tw] OR "Heptafluoro-1-butanoic acid"[tw] OR "Heptafluorobutanoic acid"[tw] OR "Heptafluorobutyric acid"[tw] OR "Perfluorobutanoic acid"[tw] OR "Perfluoropropanecarboxylic acid"[tw]) NOT medline[sb]) OR (("PFOA"[tw] OR "PFOS"[tw] OR "Pfua"[tw] OR "pfdoa"[tw] OR "C11-PFA"[tw] OR "pfsoa"[tw] OR "pfna"[tw] OR "Pfhpa"[tw] OR "pfbus"[tw] OR "PFDA"[tw] OR "pfdea"[tw] OR "Ndfda"[tw]) NOT medline[sb]) |
| **Toxcenter** | |
| 9/11/2018 | FILE 'TOXCENTER' ENTERED AT 15:57:25 ON 11 SEP 2018<br>CHARGED TO COST=EH011.10.LB.01.05<br>L1 7667 SEA FILE=TOXCENTER 1763-23-1 OR 2058-94-8 OR 2355-31-9 OR 2991-50-6 OR 307-55-1 OR 335-67-1 OR 335-76-2 OR 355-46-4 OR 375-22-4 OR 375-73-5 OR 375-85-9 OR 375-95-1 OR 754-91-6<br>L2 1413 SEA FILE=TOXCENTER 307-24-4 OR 3825-26-1<br>L4 189 SEA FILE=TOXCENTER L2 NOT L1<br>L5 7856 SEA FILE=TOXCENTER L1 OR L2<br>L6 7800 SEA FILE=TOXCENTER L5 NOT TSCATS/FS<br>L7 7460 SEA FILE=TOXCENTER L6 NOT PATENT/DT<br>ACTIVATE TOXQUERY/Q<br>---------<br>L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)<br>L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)<br>L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)<br>L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT<br>L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)<br>L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)<br>L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) |
| | L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) |
| | L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) |
| | L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) |
| | L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) |
| | L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) |
| | L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) |
| | L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) |
| | L23 QUE (ENDOCRIN? AND DISRUPT?) |
| | L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) |
| | L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) |
| | L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) |
| | L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) |
| | L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) |
| | L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) |
| | L30 QUE (NEPHROTOX? OR HEPATOTOX?) |
| | L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) |
| | L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) |
| | L33 QUE L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 |
| | L34 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) |
| | L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) |
| | L36 QUE L33 OR L34 OR L35 |
| | L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) |
| | L38 QUE L36 OR L37 |
| | --- |
| | L39 5371 SEA FILE=TOXCENTER L7 AND L38 |
| | L40 1566 SEA FILE=TOXCENTER L39 AND MEDLINE/FS |
| | L41 1116 SEA FILE=TOXCENTER L39 AND BIOSIS/FS |
| | L42 2649 SEA FILE=TOXCENTER L39 AND CAPLUS/FS |
| | L43 40 SEA FILE=TOXCENTER L39 NOT (L40 OR L41 OR L42) |
| | L44 3543 DUP REM L40 L41 L43 L42 (1828 DUPLICATES REMOVED) |
| | ANSWERS '1-3543' FROM FILE TOXCENTER |
| | L*** DEL 1566 S L39 AND MEDLINE/FS |
| | L*** DEL 1566 S L39 AND MEDLINE/FS |
| | L45 1566 SEA FILE=TOXCENTER L44 |
| | L*** DEL 1116 S L39 AND BIOSIS/FS |
| | L*** DEL 1116 S L39 AND BIOSIS/FS |
| | L46 594 SEA FILE=TOXCENTER L44 |
| | L*** DEL 2649 S L39 AND CAPLUS/FS |
| | L*** DEL 2649 S L39 AND CAPLUS/FS |
| | L47 1350 SEA FILE=TOXCENTER L44 |
| | L*** DEL 40 S L39 NOT (L40 OR L41 OR L42) |
| | L*** DEL 40 S L39 NOT (L40 OR L41 OR L42) |
| | L48 33 SEA FILE=TOXCENTER L44 |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | L49 865 SEA FILE=TOXCENTER (L45 OR L46 OR L47 OR L48) AND (ED>20160401 OR PY>2015)<br>L*** DEL 1566 S L39 AND MEDLINE/FS<br>L*** DEL 1566 S L39 AND MEDLINE/FS<br>L50 1566 SEA FILE=TOXCENTER L44<br>L*** DEL 1116 S L39 AND BIOSIS/FS<br>L*** DEL 1116 S L39 AND BIOSIS/FS<br>L51 594 SEA FILE=TOXCENTER L44<br>L*** DEL 2649 S L39 AND CAPLUS/FS<br>L*** DEL 2649 S L39 AND CAPLUS/FS<br>L52 1350 SEA FILE=TOXCENTER L44<br>L*** DEL 40 S L39 NOT (L40 OR L41 OR L42)<br>L*** DEL 40 S L39 NOT (L40 OR L41 OR L42)<br>L53 33 SEA FILE=TOXCENTER L44<br>L54 2678 SEA FILE=TOXCENTER (L50 OR L51 OR L52 OR L53) NOT L49<br>L55 43 SEA FILE=TOXCENTER L54 AND L4<br>L56 908 SEA FILE=TOXCENTER L49 OR L55<br>SAVE TEMP L56 PFOA/Q<br>D SCAN L56 |
| 05/25/2016 | FILE 'TOXCENTER' ENTERED AT 08:37:55 ON 25 MAY 2016<br>L1 5994 SEA 335-67-1 OR 1763-23-1 OR 355-46-4 OR 2991-50-6 OR 2355-31-9 OR 335-76-2 OR 375-73-5 OR 375-85-9 OR 375-95-1 OR 754-91-6 OR 2058-94-8 OR 307-55-1 OR 375-22-4<br>L2 5967 SEA L1 NOT TSCATS/FS<br>L3 5731 SEA L2 NOT PATENT/DT<br>L4 1847 SEA L3 AND ED>=20130701<br>ACT TOXQUERY/Q<br>L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)<br>L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)<br>L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)<br>L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT<br>L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)<br>L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)<br>L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)<br>L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))<br>L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)<br>L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)<br>L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)<br>L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)<br>L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)<br>L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)<br>L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)<br>L20 QUE (ENDOCRIN? AND DISRUPT?)<br>L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)<br>L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)<br>L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)<br>L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) |
| | L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) |
| | L27 QUE (NEPHROTOX? OR HEPATOTOX?) |
| | L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) |
| | L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) |
| | L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 |
| | L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) |
| | L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) |
| | L33 QUE L30 OR L31 OR L32 |
| | L34 QUE (NONHUMAN MAMMALS)/ORGN |
| | L35 QUE L33 OR L34 |
| | L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) |
| | L37 QUE L35 OR L36 |
| | L38 1318 SEA L4 AND L37 |
| | L39 1148 SEA L4 AND L30 |
| | L40 356 SEA L38 AND MEDLINE/FS |
| | L41 297 SEA L38 AND BIOSIS/FS |
| | L42 664 SEA L38 AND CAPLUS/FS |
| | L43 1 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L44 931 DUP REM L40 L41 L43 L42 (387 DUPLICATES REMOVED) |
| | L*** DEL 356 S L38 AND MEDLINE/FS |
| | L*** DEL 356 S L38 AND MEDLINE/FS |
| | L45 356 SEA L44 |
| | L*** DEL 297 S L38 AND BIOSIS/FS |
| | L*** DEL 297 S L38 AND BIOSIS/FS |
| | L46 190 SEA L44 |
| | L*** DEL 664 S L38 AND CAPLUS/FS |
| | L*** DEL 664 S L38 AND CAPLUS/FS |
| | L47 385 SEA L44 |
| | L48 575 SEA (L45 OR L46 OR L47) NOT MEDLINE/FS |
| | D SCAN L48 |
| 09/19/2013 | FILE 'TOXCENTER' ENTERED AT 09:10:51 ON 19 SEP 2013 |
| | L1 3993 SEA 335-67-1 OR 1763-23-1 OR 355-46-4 OR 2991-50-6 OR 2355-31-9 OR 335-76-2 OR 375-73-5 OR 375-85-9 OR 375-95-1 OR 754-91-6 OR 2058-94-8 OR 307-55-1 OR 375-22-4 |
| | L2 3966 SEA L1 NOT TSCATS/FS |
| | L3 3782 SEA L2 NOT PATENT/DT |
| | L4 2796 SEA L3 AND PY>2006 |
| | ACTIVATE TOXBROAD/Q |
| | L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) |
| | L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT) |
| | L7 QUE (ACUTE OR SUBACUTE OR LD50 OR LC50) |
| | L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT |
| | L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) |
| | L10 QUE (VAPOR? OR VAPOUR? OR AEROSOL?) |
| | L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) |
| | L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET? OR DRINKING(W)WATER?) |
| | L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) |
| | L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) |
| | L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) |
| | L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) |
| | L18 QUE (SPERM? OR NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMEN TAL?) |
| | L19 QUE (ENDOCRIN? AND DISRUPT?) |
| | L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) |
| | L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) |
| | L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) |
| | L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) |
| | L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) |
| | L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN?) |
| | L26 QUE GENETIC(W)TOXIC? |
| | L27 QUE L5 OR L6 OR L7 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 |
| | L28 QUE L27 OR L22 OR L23 OR L24 OR L25 OR L26 |
| | L29 QUE L28 OR L8 |
| | L30 QUE NEPHROTOX? OR HEPATOTOX? OR ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON? |
| | L31 QUE L29 OR L30 |
| | L32 QUE RAT OR RATS OR MOUSE OR MICE OR GUINEA PIG OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR GOAT OR GOATS OR SHEEP OR MONKEY? OR MACAQUE? |
| | L33 QUE MARMOSET? OR FERRET? OR GERBIL? OR HAMSTER? OR RODENT? OR LAGOMORPHA OR BABOON? OR BOVINE OR CANINE OR CAT OR CATS OR FELINE OR PIGEON? |
| | L34 QUE OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM? |
| | L35 QUE L31 OR L32 OR L33 OR L34 |
| | L36 QUE NONHUMAN MAMMALS/ORGN |
| | L37 QUE L35 OR L36 |
| | L38 QUE HUMAN? OR HOMINIDAE OR MAMMAL? OR PRIMATE? |
| | L39 QUE L37 OR L38 |
| | L40 2012 SEA L4 AND L39 |
| | L41 619 SEA L40 AND MEDLINE/FS |
| | L42 417 SEA L40 AND BIOSIS/FS |
| | L43 975 SEA L40 AND CAPLUS/FS |
| | L44 1 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L45 1308 DUP REM L41 L42 L44 L43 (704 DUPLICATES REMOVED) |
| | L*** DEL 619 S L40 AND MEDLINE/FS |
| | L*** DEL 619 S L40 AND MEDLINE/FS |
| | L46 619 SEA L45 |
| | L*** DEL 417 S L40 AND BIOSIS/FS |
| | L*** DEL 417 S L40 AND BIOSIS/FS |
| | L47 217 SEA L45 |
| | L*** DEL 975 S L40 AND CAPLUS/FS |
| | L*** DEL 975 S L40 AND CAPLUS/FS |
| | L48 471 SEA L45 |
| | L*** DEL 1 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L*** DEL 1 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) |
| | L49 1 SEA L45 |
| | L50 689 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | SAVE TEMP L50 PERFLUOROALKYLS/A PFOA/A<br>L51 217 SEA L50 AND BIOSIS/FS<br>L52 471 SEA L50 AND CAPLUS/FS<br>L53 220 SEA L52 AND 4-?/CC<br>L54 1 SEA L50 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)<br>L55 438 SEA L51 OR L53 OR L54<br>L56 689 SEA L55 OR L52<br>D SCAN L55 |
| **ToxLine** | |
| 9/11/2018 | ( 1763-23-1 [rn] OR 2058-94-8 [rn] OR 2355-31-9 [rn] OR 2991-50-6 [rn] OR 307-55-1 [rn] OR 335-67-1 [rn] OR 335-76-2 [rn] OR 355-46-4 [rn] OR 375-22-4 [rn] OR 375-73-5 [rn] OR 375-85-9 [rn] OR 375-95-1 [rn] OR 754-91-6 [rn] ) AND 2015:2017 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org] |
| | ( "perfluoro n heptanoic acid" OR "perfluoro n nonanoic acid" OR "perfluoro n undecanoic acid" OR "perfluorobutane sulfonic acid" OR "perfluorobutanesulfonic acid" OR "perfluorobutanoic acid" OR "perfluorobutyric acid" OR "perfluorocaprylic acid" OR "perfluorooctanoic acid" OR "perfluorooctylsulfonamide" OR "perfluorodecanoic acid" OR "perfluorododecanoic acid" OR "perfluorododecanoic acid " OR "perfluoroheptanecarboxylic acid" OR "perfluoroheptanoic acid" OR "perfluorohexane sulfonic acid" OR "perfluorohexane 1 sulphonic acid" OR "perfluorohexanesulfonate" OR "perfluorohexanesulfonic acid" OR "perfluorolauric acid" OR "perfluorononan 1 oic acid" OR "perfluorononanoic acid" OR "perfluorooctane sulfonamide" OR "perfluorooctane sulfonate" OR "perfluorooctane sulfonic acid " OR "perfluorooctane sulphonic acid" OR "perfluorooctanesulfonamide" OR "perfluorooctanesulfonate" OR "perfluorooctanesulfonic acid" OR "perfluorooctanesulfonic acid amide" OR "perfluorooctanoic acid" OR "perfluorooctylsulfonic acid" OR "perfluoropropanecarboxylic acid" OR "perfluoroundecanoic acid" OR "pfbus" OR "pfda" OR "pfdea" OR "pfdoa" OR "pfhpa" OR "pfhs cpd" OR "pfhxs" OR "pfna" OR "pfoa" OR "pfos" OR "pfsoa" OR "pfua" OR "tricosafluorododecanoic acid" OR "tridecafluoro 1 heptanoic acid" OR "tridecafluoroheptanoic acid" ) AND 2015:2017 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org] |
| | ( "1 1 2 2 3 3 4 4 4 nonafluoro 1 butanesulfonic acid" OR "1 1 2 2 3 3 4 4 4 nonafluorobutane 1 sulphonic acid" OR "1 1 2 2 3 3 4 4 5 5 6 6 6 tridecafluorohexane 1 sulfonic acid" OR "1 perfluorobutanesulfonic acid" OR "2 2 3 3 4 4 5 5 6 6 7 7 8 8 9 9 9 heptadecafluoro nonanoic acid" OR "2 ( n ethyl perfluorooctane sulfonamido ) acetic acid" OR "2 ( n methyl perfluorooctane sulfonamido ) acetic acid" OR "c11 pfa" OR "et pfosa acoh" OR "glycine n ethyl n ( ( 1 1 2 2 3 3 4 4 5 5 6 6 7 7 8 8 8 heptadecafluorooctyl ) sulfonyl ) " OR "henicosafluoroundecanoic acid" OR "heptadecafluoro 1 octane sulfonic acid" OR "heptadecafluoro 1 octanesulfonic acid" OR "heptadecafluorooctane sulfonic acid" OR "heptadecafluorooctane 1 sulphonic acid" OR "heptadecafluorooctanesulphonamide" OR "heptafluoro 1 butanoic acid" OR "heptafluorobutanoic acid" OR "heptafluorobutyric acid" OR "me pfosa acoh" OR "n ethyl n ( ( heptadecafluorooctyl ) sulphonyl ) glycine" OR "ndfda" OR "nonadecafluoro n decanoic acid" OR "nonadecafluorodecanoic acid" OR "nonafluoro 1 butanesulfonic acid" OR "nonafluorobutanesulfonic acid" OR "pentadecafluoro 1 octanoic acid" OR "pentadecafluoro n octanoic acid" OR "pentadecafluorooctanoic acid" OR "pentyl perfluorobutanoate" OR "perfluoro n decanoic acid" ) AND 2015:2017 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org] |
| | ( 307-24-4 [rn] OR 3825-26-1 [rn] OR "hexanoic acid 2 2 3 3 4 4 5 5 6 6 6-undecafluoro-" OR "hexanoic acid undecafluoro-" OR "perfluorohexanoic acid" OR "undecafluoro-1-hexanoic acid" OR "undecafluorohexanoic acid" OR "ammonium pentadecafluorooctanoate" OR "ammonium |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | perfluorocaprilate" OR "ammonium perfluorocaprylate" OR "ammonium perfluorooctanoate" OR "fc 143" OR "octanoic acid 2 2 3 3 4 4 5 5 6 6 7 7 8 8 8-pentadecafluoro- ammonium salt" OR "octanoic acid pentadecafluoro- ammonium salt" OR "pentadecafluoro-1-octanoic acid ammonium salt" OR "pentadecafluorooctanoic acid ammonium salt" OR "perfluoroammonium octanoate" OR "perfluorooctanoic acid ammonium salt" ) AND 1900:2017 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org] |
| 05/24/2016 | ((("C11-PFA" OR "et-pfosa-acoh" OR "Henicosafluoroundecanoic acid" OR "heptadecafluoro-1-octane sulfonic acid" OR "Heptadecafluoro-1-octanesulfonic acid" OR "heptadecafluorooctane sulfonic acid" OR "Heptadecafluorooctane-1-sulphonic acid" OR "Heptadecafluorooctane-1-sulphonic acid1-Perfluorooctanesulfonic acid" OR "Heptadecafluorooctanesulphonamide" OR "Heptafluoro-1-butanoic acid" OR "Heptafluorobutanoic acid" OR "Heptafluorobutyric acid" OR "me-pfosa-acoh" OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine" OR "Ndfda" OR "Nonadecafluoro-n-decanoic acid" OR "Nonadecafluorodecanoic acid" OR "Nonafluoro-1-butanesulfonic acid" OR "Nonafluorobutanesulfonic acid" OR "Pentadecafluoro-1-octanoic acid" OR "Pentadecafluoro-n-octanoic acid" OR "Pentadecafluorooctanoic acid" OR "Pentyl perfluorobutanoate" OR "Perfluoro-n-decanoic acid" OR "Perfluoro-n-heptanoic acid" OR "Perfluoro-n-nonanoic acid" OR "Perfluoro-n-undecanoic acid" OR "Perfluorobutane sulfonic acid" OR "Perfluorobutanesulfonic acid" OR "Perfluorobutanoic acid" OR "Perfluorobutyric acid" OR "Perfluorocaprylic acid" OR "Perfluorooctanoic acid" OR "Perfluorooctylsulfonamide" OR "Perfluorodecanoic acid" OR "Perfluorododecanoic acid " OR "Perfluorododecanoic acid" OR "Perfluoroheptanecarboxylic acid" OR "Perfluoroheptanoic acid" OR "Perfluorohexane sulfonic acid" OR "Perfluorohexane-1-sulphonic acid" OR "perfluorohexanesulfonate" OR "perfluorohexanesulfonic acid" OR "Perfluorolauric acid" OR "Perfluorononan-1-oic acid" OR "Perfluorononanoic acid" OR "Perfluorooctane sulfonamide" OR "Perfluorooctane sulfonate" OR "Perfluorooctane sulfonic acid " OR "perfluorooctane sulphonic acid" OR "Perfluorooctanesulfonamide" OR "Perfluorooctanesulfonate" OR "Perfluorooctanesulfonic acid amide" OR "perfluorooctanesulfonic acid" OR "Perfluorooctanoic acid" OR "Perfluorooctylsulfonic acid" OR "Perfluoropropanecarboxylic acid" OR "Perfluoroundecanoic acid" OR "pfbus" OR "PFDA" OR "pfdea" OR "pfdoa" OR "Pfhpa" OR "PFHS cpd" OR "pfhxs" OR "pfna" OR "PFOA" OR "PFOS" OR "pfsoa" OR "Pfua" OR "Tricosafluorododecanoic acid" OR "Tridecafluoro-1-heptanoic acid" OR "Tridecafluoroheptanoic acid") AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) OR ("1763-23-1" OR "2058-94-8" OR "2355-31-9" OR "2991-50-6" OR "307-55-1" OR "335-67-1" OR "335-76-2" OR "355-46-4" OR "375-22-4" OR "375-73-5" OR "375-85-9" OR "375-95-1" OR "754-91-6") AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ))) AND 2013:2016 [yr]<br><br>("1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid" OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid" OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid" OR "1-Perfluorobutanesulfonic acid" OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid" OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid" OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid" OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-") AND 2013:2016 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) |
| 09/18/2013 | ( "perfluorooctanoic acid" OR "pentadecafluoro 1 octanoic acid" OR "pentadecafluoro n octanoic acid" OR "pentadecafluorooctanoic acid" OR "perfluorocaprylic acid" OR "perfluoroctanoic acid" OR "perfluoroheptanecarboxylic acid" OR "perfluorooctanoic acid" OR "pentadecafluorooctanoic acid" OR "perfluorooctanoic acid" OR "perfluorooctane sulfonic acid " OR "heptadecafluoro 1 octanesulfonic acid" OR "heptadecafluoro 1 octane sulfonic acid" OR "heptadecafluorooctane 1 sulphonic acid" OR "heptadecafluorooctane sulfonic acid" OR "perfluorooctane sulfonate" OR "perfluorooctylsulfonic acid" OR "perfluorooctane sulphonic acid" OR "perfluorooctanesulfonic acid" |

## Table B-2. Database Query Strings Post Public Comment Searches

| Database search date | Query string |
|---|---|
| | OR "perfluorooctanesulfonate" OR "heptadecafluorooctane 1 sulphonic acid1 perfluorooctanesulfonic acid" OR "perfluorohexane sulfonic acid pfhxs " OR "perfluorohexanesulfonic acid" OR "perfluorohexanesulfonate" OR "perfluorohexane 1 sulphonic acid" OR "pfhs cpd" OR "2 ( n ethyl perfluorooctane sulfonamido ) acetic acid" OR "et pfosa acoh" OR "n ethyl n ( ( heptadecafluorooctyl ) sulphonyl ) glycine" OR "2 ( n methyl perfluorooctane sulfonamido ) acetic acid" OR "me pfosa acoh" OR "perfluorodecanoic acid" OR "nonadecafluoro n decanoic acid" OR "nonadecafluorodecanoic acid" OR "perfluoro n decanoic acid" OR "perfluoro n decanoic acid" OR "perfluorodecanoic acid" OR "nonadecafluorodecanoic acid" OR "perfluoro n decanoic acid" OR "perfluorobutane sulfonic acid" OR "perfluorobutanesulfonic acid" OR OR "pentyl perfluorobutanoate" OR "nonafluoro 1 butanesulfonic acid" OR "perfluoroheptanoic acid" OR "tridecafluoro 1 heptanoic acid" OR "perfluoro n heptanoic acid" OR "perfluoroheptanoic acid" OR "tridecafluoroheptanoic acid" OR "perfluorononanoic acid" OR "perfluoro n nonanoic acid" OR "perfluorononan 1 oic acid" OR "perfluorooctane sulfonamide" OR "perfluorooctanesulfonamide" OR "perfluoroctylsulfonamide" OR "perfluorooctanesulfonic acid amide" OR "heptadecafluorooctanesulphonamide" OR "perfluoroundecanoic acid" OR "perfluoro n undecanoic acid" OR "hennone ) AND 2007:2013 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR NIH RePORTER [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) NOT PubMed [org] NOT pubdart [org] |

## Table B-3. Strategies to Augment the Literature Search

| Source | Query and number screened when available |
|---|---|
| **TSCATS[a]** | |
| 9/11/2018<br>5/23/2016<br>9/18/2013 | Compounds searched: 1763-23-1; 2058-94-8; 2355-31-9; 2991-50-6; 307-55-1; 335-67-1; 335-76-2; 355-46-4; 375-22-4; 375-73-5; 375-85-9; 375-95-1; 754-91-6; 307-24-4; 3825-26-1 |
| **NTP** | |
| 9/11/2018 | Content types: Reports & Publications; Systematic Reviews; ROC Profiles, Reviews or Candidates; Testing Status<br>"1763-23-1" "2058-94-8" "2355-31-9" "2991-50-6" "307-55-1" "335-67-1" "335-76-2" "355-46-4" "375-22-4" "375-73-5" "375-85-9" "375-95-1" "754-91-6" "Henicosafluoroundecanoic acid" "heptadecafluoro-1-octane sulfonic acid" "Heptadecafluoro-1-octanesulfonic acid" "heptadecafluorooctane sulfonic acid" "Heptadecafluorooctane-1-sulphonic acid" "Heptadecafluorooctanesulphonamide" "Heptafluoro-1-butanoic acid" "Heptafluorobutanoic acid" "Heptafluorobutyric acid" "me-pfosa-acoh" "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine" "Ndfda" "Nonadecafluoro-n-decanoic acid" "Nonadecafluorodecanoic acid" "Nonafluoro-1-butanesulfonic acid" "Nonafluorobutanesulfonic acid" "Pentadecafluoro-1-octanoic acid" "Pentadecafluoro-n-octanoic acid" "Pentadecafluorooctanoic acid" "Pentyl perfluorobutanoate" "Perfluoro-n-decanoic acid" "Perfluoro-n-heptanoic acid" "Perfluoro-n-nonanoic acid" "Perfluoro-n-undecanoic acid" "Perfluorobutane sulfonic acid" "Perfluorobutanesulfonic acid" "Perfluorobutanoic acid" "Perfluorobutyric acid" "Perfluorocaprylic acid" "Perfluoroctanoic acid" "Perfluoroctylsulfonamide" "Perfluorodecanoic acid" "Perfluorododecanoic acid" "Perfluorododecanoic acid " "Perfluoroheptanecarboxylic acid" "Perfluoroheptanoic acid" "Perfluorohexane sulfonic acid" "Perfluorohexane-1-sulphonic acid" "perfluorohexanesulfonate" "perfluorohexanesulfonic acid" "Perfluorolauric acid" "Perfluorononan-1-oic acid" "Perfluorononanoic acid" "Perfluorooctane sulfonamide" "Perfluorooctane sulfonate" "Perfluorooctane sulfonic acid " "perfluorooctane sulphonic acid" "Perfluorooctanesulfonamide" "Perfluorooctanesulfonate" "perfluorooctanesulfonic acid" "Perfluorooctanesulfonic acid amide" "Perfluorooctanoic acid" "Perfluorooctylsulfonic acid" "Perfluoropropanecarboxylic acid" "Perfluoroundecanoic acid" "pfbus" "PFDA" "pfdea" "pfdoa" "Pfhpa" "PFHS cpd" "pfhxs" "pfna" "PFOA" "PFOS" "pfsoa" |

## Table B-3. Strategies to Augment the Literature Search

| Source | Query and number screened when available |
|---|---|
| | "Pfua" "Tricosafluorododecanoic acid" "Tridecafluoro-1-heptanoic acid" "Tridecafluoroheptanoic acid"<br>"307-24-4" "3825-26-1"<br>"Perfluorohexanoic acid" "Undecafluoro-1-hexanoic acid" "Undecafluorohexanoic acid" "Ammonium pentadecafluorooctanoate" "Ammonium perfluorocaprilate" "Ammonium perfluorocaprylate" "Ammonium perfluorooctanoate" "FC 143" "Octanoic acid, pentadecafluoro-, ammonium salt" "Pentadecafluoro-1-octanoic acid, ammonium salt" "Pentadecafluorooctanoic acid, ammonium salt" "Perfluoroammonium octanoate" "Perfluorooctanoic acid, ammonium salt" |
| 5/23/2016 | "335-67-1" OR "1763-23-1" OR "355-46-4" OR "2991-50-6" OR "2355-31-9" OR "335-76-2" OR "375-73-5" OR "375-85-9" OR "375-95-1" OR "754-91-6" OR "2058-94-8" OR "307-55-1" OR "375-22-4" OR "Perfluorooctanoic acid" OR "PFOA" OR "Pentadecafluoro-1-octanoic acid" OR "Pentadecafluorooctanoic acid" OR "Perfluoroctanoic acid" OR "Perfluorooctane sulfonic acid" OR "Heptadecafluorooctane-1-sulphonic acid" OR "PFOS" OR "Perfluorooctane sulfonate" OR "Perfluorooctylsulfonic acid" OR "perfluorooctane sulphonic acid" OR "perfluorooctanesulfonic acid" OR "Perfluorooctanesulfonate" OR "Heptadecafluorooctane-1-sulphonic acid" OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid" OR "Perfluorohexane sulfonic acid" OR "Perfluorohexane-1-sulphonic acid" OR "perfluorohexanesulfonate" OR "perfluorohexanesulfonic acid" OR "pfhxs" OR "Ndfda" OR "Nonadecafluorodecanoic acid" OR "Nonadecafluoro-n-decanoic acid" OR "Perfluorodecanoic acid" OR "Perfluoro-n-decanoic acid" OR "PFDA" OR "pfdea" OR "1-Perfluorobutanesulfonic acid" OR "Nonafluoro-1-butanesulfonic acid" OR "Perfluorobutane sulfonic acid" OR "Perfluorobutanesulfonic acid" OR "pfbus" OR "Perfluorononanoic acid" OR "pfna" OR "Perfluorooctanesulfonamide" OR "Perfluorododecanoic acid" OR "pfdoa" OR "Heptafluorobutyric acid" OR "Perfluorobutanoic acid" OR "Perfluorobutyric acid"<br>Screened: 146 hits |
| | "1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid" OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid" OR "Nonafluorobutanesulfonic acid" OR "Pentyl perfluorobutanoate" OR "Pentadecafluoro-n-octanoic acid" OR "Perfluorocaprylic acid" OR "Perfluoroheptanecarboxylic acid" OR "Heptadecafluoro-1-octanesulfonic acid" OR "heptadecafluoro-1-octane sulfonic acid" OR "heptadecafluorooctane sulfonic acid" OR "1-Perfluorooctanesulfonic acid" OR "PFHS cpd" OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid" OR "et-pfosa-acoh" OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine" OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-" OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid" OR "me-pfosa-acoh" OR "Perfluoroheptanoic acid" OR "Perfluoro-n-heptanoic acid" OR "Pfhpa" OR "Tridecafluoro-1-heptanoic acid" OR "Tridecafluoroheptanoic acid" OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid" OR "Perfluoro-n-nonanoic acid" OR "Perfluorononan-1-oic acid" OR "Heptadecafluorooctanesulphonamide" OR "Perfluoroctylsulfonamide" OR "Perfluorooctane sulfonamide" OR "Perfluorooctanesulfonic acid amide" OR "Pfsoa" OR "C11-PFA" OR "Henicosafluoroundecanoic acid" OR "Perfluoro-n-undecanoic acid" OR "Perfluoroundecanoic acid" OR "Pfua" OR "Perfluorolauric acid" OR "Tricosafluorododecanoic acid" OR "Heptafluoro-1-butanoic acid" OR "Heptafluorobutanoic acid" OR "Perfluoropropanecarboxylic acid"<br>Screened: 0 hits |

## Table B-3. Strategies to Augment the Literature Search

| Source | Query and number screened when available |
|---|---|
| **NIH RePORTER** | |
| 2/28/2017 | Text Search: "1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonic acid" OR "1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulphonic acid" OR "1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid" OR "1-Perfluorobutanesulfonic acid" OR "2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-Nonanoic acid" OR "2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid" OR "2-(N-Methyl-perfluorooctane sulfonamido) acetic acid" OR "C11-PFA" OR "et-pfosa-acoh" OR "Glycine, N-ethyl-N-((1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl)-" OR "Henicosafluoroundecanoic acid" OR "heptadecafluoro-1-octane sulfonic acid" OR "Heptadecafluoro-1-octanesulfonic acid" OR "heptadecafluorooctane sulfonic acid" OR "Heptadecafluorooctane-1-sulphonic acid" OR "Heptadecafluorooctanesulphonamide" OR "Heptafluoro-1-butanoic acid" OR "Heptafluorobutanoic acid" OR "Heptafluorobutyric acid" OR "me-pfosa-acoh" OR "N-Ethyl-N-((heptadecafluorooctyl)sulphonyl)glycine" OR "Ndfda" OR "Nonadecafluoro-n-decanoic acid" OR "Nonadecafluorodecanoic acid" OR "Nonafluoro-1-butanesulfonic acid" OR "Nonafluorobutanesulfonic acid" OR "Pentadecafluoro-1-octanoic acid" OR "Pentadecafluoro-n-octanoic acid" OR "Pentadecafluorooctanoic acid" OR "Pentyl perfluorobutanoate" OR "Perfluoro-n-decanoic acid" OR "Perfluoro-n-heptanoic acid" OR "Perfluoro-n-nonanoic acid" OR "Perfluoro-n-undecanoic acid" OR "Perfluorobutane sulfonic acid" OR "Perfluorobutanesulfonic acid" OR "Perfluorobutanoic acid" OR "Perfluorobutyric acid" OR "Perfluorocaprylic acid" OR "Perfluoroctanoic acid" OR "Perfluoroctylsulfonamide" OR "Perfluorodecanoic acid" OR "Perfluorododecanoic acid" OR "Perfluorododecanoic acid" OR "Perfluoroheptanecarboxylic acid" OR "Perfluoroheptanoic acid" OR "Perfluorohexane sulfonic acid" OR "Perfluorohexane-1-sulphonic acid" OR "perfluorohexanesulfonate" OR "perfluorohexanesulfonic acid" OR "Perfluorolauric acid" OR "Perfluorononan-1-oic acid" OR "Perfluorononanoic acid" OR "Perfluorooctane sulfonamide" OR "Perfluorooctane sulfonate" OR "Perfluorooctane sulfonic acid" OR "perfluorooctane sulphonic acid" OR "Perfluorooctanesulfonamide" OR "Perfluorooctanesulfonate" OR "Perfluorooctanesulfonic acid amide" OR "perfluorooctanesulfonic acid" OR "Perfluorooctanoic acid" OR "Perfluorooctylsulfonic acid" OR "Perfluoropropanecarboxylic acid" OR "Perfluoroundecanoic acid" OR "pfbus" OR "PFDA" OR "pfdea" OR "pfdoa" OR "Pfhpa" OR "PFHS cpd" OR "pfhxs" OR "pfna" OR "PFOA" OR "PFOS" OR "pfsoa" OR "Pfua" OR "Tricosafluorododecanoic acid" OR "Tridecafluoro-1-heptanoic acid" OR "Tridecafluoroheptanoic acid" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects, 2017, 2016, 2015, 2014, 2013, 2012<br>Screened: 80 |
| 4/7/2014 | Compounds searched: 335-67-1; 1763-23-1; 355-46-4; 2991-50-6; 2355-31-9; 335-76-2; 375-73-5; 375-85-9; 375-95-1; 754-91-6; 2058-94-8; 307-55-1; 375-22-4<br>Screened: 82 hits |
| **Other** | Identified throughout the assessment process |

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The September 2018 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 941
- Number of records identified from other strategies: 153
- Total number of records to undergo literature screening: 1,094

### B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on perfluoroalkyls:

- Title and abstract screen
- Full text screen

***Title and Abstract Screen.*** Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

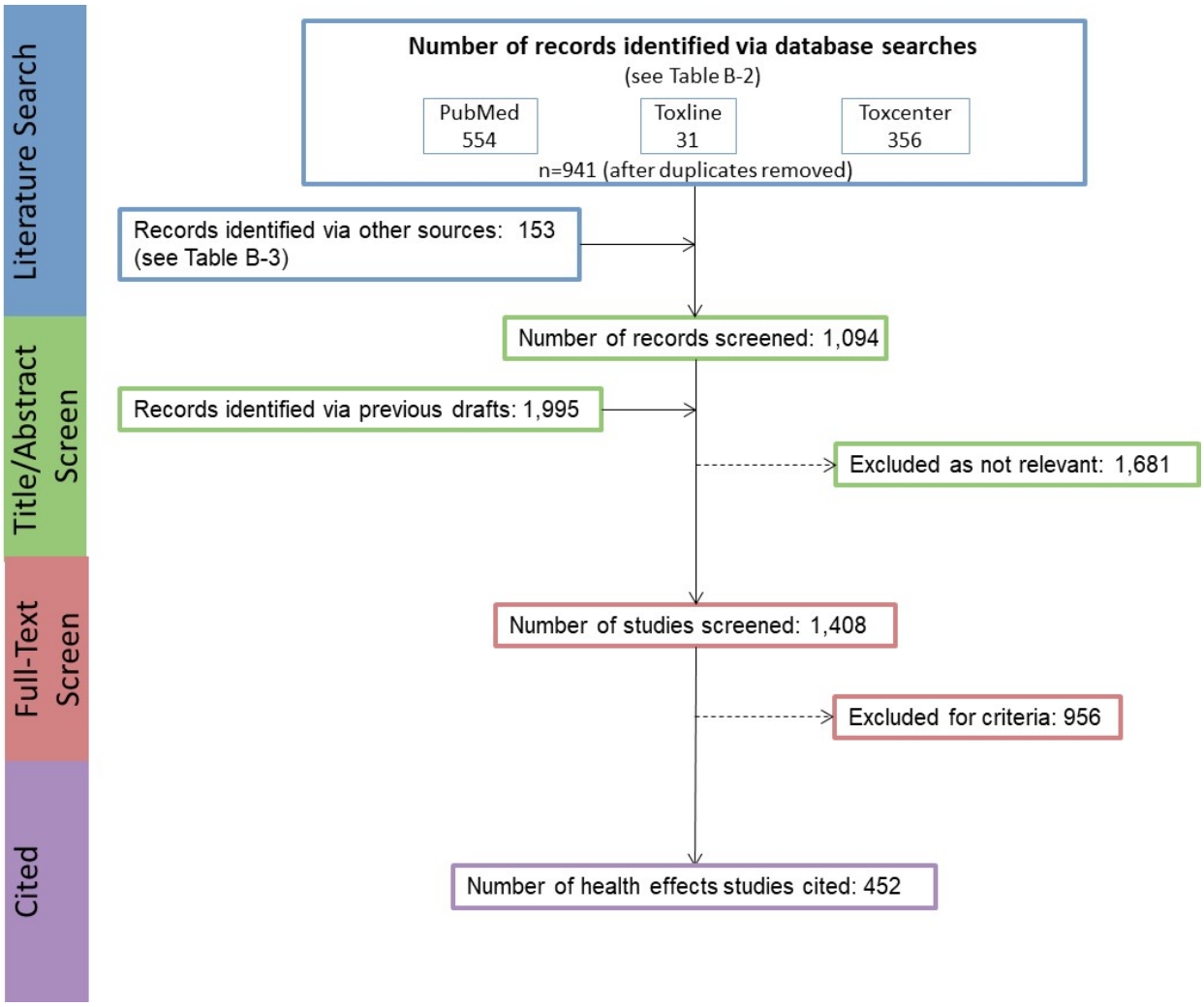
- Number of titles and abstracts screened: 1,094
- Number of studies considered relevant and moved to the next step: 1,408

***Full Text Screen.*** The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 1,408
- Total number of health effects studies cited in the profile: 452

A summary of the results of the literature search and screening is presented in Figure B-1.

**Figure B-1. September 2018 Literature Search Results and Screen for Perfluoroalkyls**



# APPENDIX C. USER'S GUIDE

## Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

### Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

**Chapter 2. Health Effects**

**Tables and Figures for Levels of Significant Exposure (LSE)**

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**TABLE LEGEND**

**See Sample LSE Table (page C-5)**

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

**FIGURE LEGEND**

**See Sample LSE Figure (page C-6)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in $mg/m^3$ or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX B

**Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral** (1)

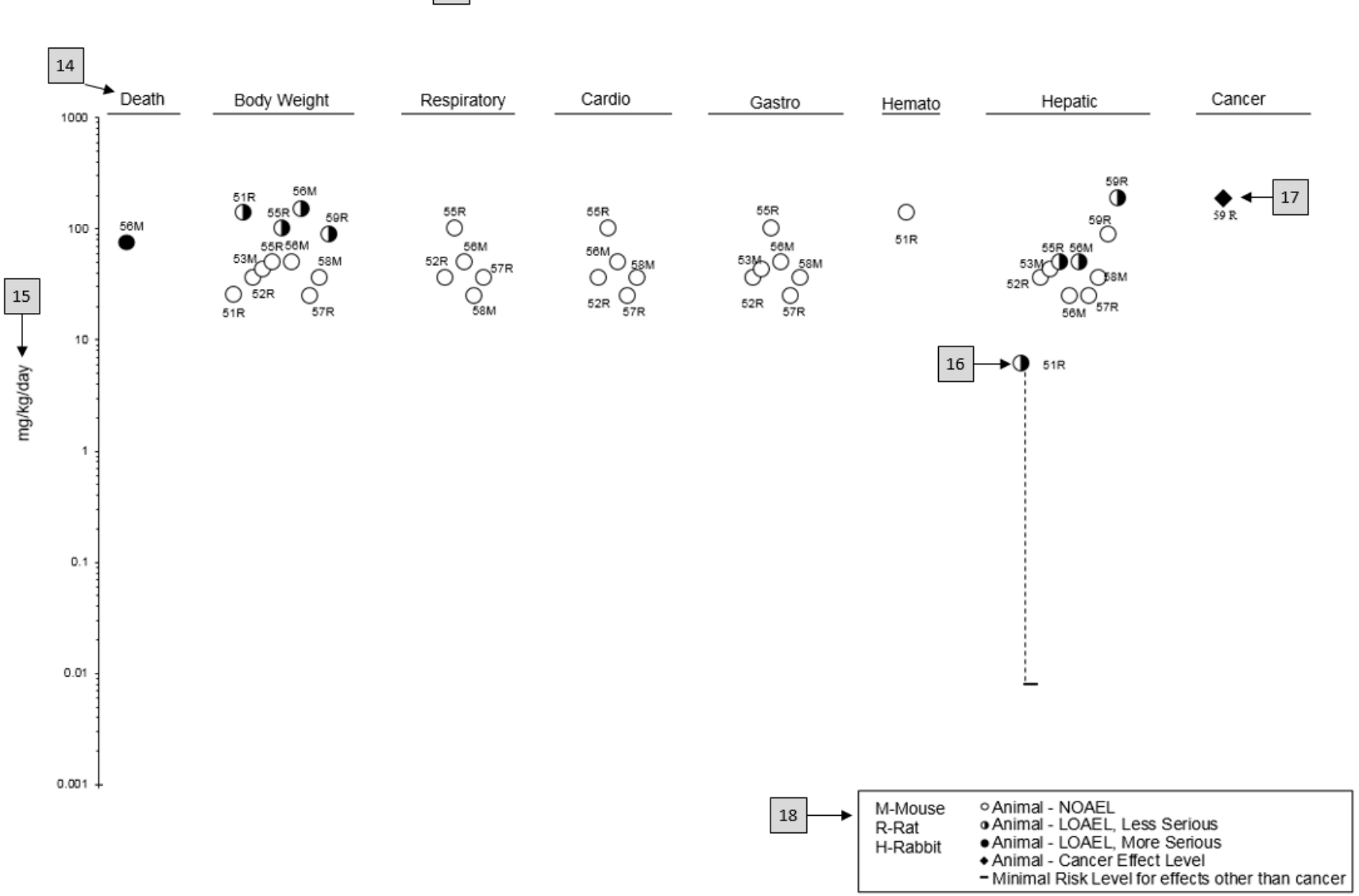
| Figure key[a] (3) | Species (strain) No./group (4) | Exposure parameters (5) | Doses (mg/kg/day) (5) | Parameters monitored (6) | Endpoint (7) | NOAEL (mg/kg/day) (8) | Less serious LOAEL (mg/kg/day) (9) | Serious LOAEL (mg/kg/day) (9) | Effect |
|---|---|---|---|---|---|---|---|---|---|
| **CHRONIC EXPOSURE** (2) | | | | | | | | | |
| 51 | Rat (Wistar) 40 M, 40 F | 2 years (F) | M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4 | CS, WI, BW, OW, HE, BC, HP | Bd wt | 25.5 | 138.0 | | Decreased body weight gain in males (23–25%) and females (31–39%) |
| | | | | | Hemato | 138.0 | | | |
| | | | | | Hepatic | | 6.1[c] | | Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure |
| **Aida et al. 1992** (10) | | | | | | | | | |
| 52 | Rat (F344) 78 M | 104 weeks (W) | 0, 3.9, 20.6, 36.3 | CS, BW, FI, BC, OW, HP | Hepatic | 36.3 | | | |
| | | | | | Renal | 20.6 | 36.3 | | Increased incidence of renal tubular cell hyperplasia |
| | | | | | Endocr | 36.3 | | | |
| **George et al. 2002** | | | | | | | | | |
| 59 | Rat (Wistar) 58M, 58F | Lifetime (W) | M: 0, 90 F: 0, 190 | BW, HP | Cancer | | 190 F | | Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided |
| **Tumasonis et al. 1985** | | | | | | | | | |

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

## Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



# APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

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***Primary Chapters/Sections of Interest***

**Chapter 1: Relevance to Public Health**: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

**Chapter 2: Health Effects**: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
***NOTE***: Not all health effects reported in this section are necessarily observed in the clinical setting.

**Pediatrics**:

**Section 3.2 Children and Other Populations that are Unusually Susceptible**
**Section 3.3 Biomarkers of Exposure and Effect**

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***ATSDR Information Center***

***Phone:*** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
***Internet***: http://www.atsdr.cdc.gov

The following additional materials are available online:

*Case Studies in Environmental Medicine* are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

*Managing Hazardous Materials Incidents* is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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***Other Agencies and Organizations***

*The National Center for Environmental Health* (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

*The National Institute for Occupational Safety and Health* (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

*The National Institute of Environmental Health Sciences* (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

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***Clinical Resources (Publicly Available Information)***

*The Association of Occupational and Environmental Clinics* (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

*The American College of Occupational and Environmental Medicine* (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

*The American College of Medical Toxicology* (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

*The Pediatric Environmental Health Specialty Units* (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

*The American Association of Poison Control Centers* (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

# APPENDIX E. GLOSSARY

**Absorption—**The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure—**Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

**Adsorption—**The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ($K_{oc}$)—**The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio (Kd)—**The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD) or Benchmark Concentration (BMC)—**is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a $BMD_{10}$ would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

**Bioconcentration Factor (BCF)—**The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers—**Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

**Cancer Effect Level (CEL)—**The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen—**A chemical capable of inducing cancer.

**Case-Control Study—**A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

**Case Report—**A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

**Case Series—**Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

**Ceiling Value—**A concentration that must not be exceeded.

**Chronic Exposure—**Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

**Clastogen—**A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

**Cohort Study—**A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

**Cross-sectional Study—**A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

**Data Needs—**Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

**Developmental Toxicity—**The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship—**The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

**Embryotoxicity and Fetotoxicity—**Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

**Epidemiology—**The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**Excretion—**The process by which metabolic waste products are removed from the body.

**Genotoxicity—**A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life—**A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

**Health Advisory—**An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Immediately Dangerous to Life or Health (IDLH)—**A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

**Immunotoxicity—**Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

**Incidence—**The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure—**Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

**Lethal Concentration$_{(LO)}$ ($LC_{LO}$)—**The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration$_{(50)}$ ($LC_{50}$)—**A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose$_{(LO)}$ ($LD_{Lo}$)—**The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose$_{(50)}$ ($LD_{50}$)—**The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time$_{(50)}$ ($LT_{50}$)—**A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)—**The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects—**Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations—**Permanent structural changes that may adversely affect survival, development, or function.

**Metabolism—**Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

**Minimal Risk Level (MRL)—**An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)—**A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity—**The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

**Mortality—**Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen—**A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy—**The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity—**The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

**No-Observed-Adverse-Effect Level (NOAEL)—**The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)—**The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)—**A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

**Permissible Exposure Limit (PEL)—**An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

**Pesticide—**General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

**Pharmacokinetics—**The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

**Pharmacokinetic Model—**A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model—**A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model—**A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence—**The number of cases of a disease or condition in a population at one point in time.

**Prospective Study—**A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

**Recommended Exposure Limit (REL)—**A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of $mg/m^3$ or ppm.

**Reference Dose (RfD)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

**Reportable Quantity (RQ)—**The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity—**The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study—**A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Reverse Causation**—Describes an association where the outcome results in a change in the biomarker of exposure.

**Risk—**The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

**Risk Factor—**An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio/Relative Risk—**The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

**Short-Term Exposure Limit (STEL)—**A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

**Standardized Mortality Ratio (SMR)—**A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity—**This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen—**A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)—**An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)—**An average exposure within a given time period.

**Toxicokinetic—**The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

**Toxics Release Inventory (TRI)—**The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

**Uncertainty Factor (UF)—**A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

**Xenobiotic—**Any substance that is foreign to the biological system.

# APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| AAPCC | American Association of Poison Control Centers |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ACMT | American College of Medical Toxicology |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AEGL | Acute Exposure Guideline Level |
| AIC | Akaike's information criterion |
| AIHA | American Industrial Hygiene Association |
| ALT | alanine aminotransferase |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| APFO | ammonium perfluorooctanoate |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BCF | bioconcentration factor |
| BMD/C | benchmark dose or benchmark concentration |
| $BMD_X$ | dose that produces a X% change in response rate of an adverse effect |
| $BMDL_X$ | 95% lower confidence limit on the $BMD_X$ |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| C | centigrade |
| CAA | Clean Air Act |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| cm | centimeter |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DWEL | drinking water exposure level |
| EAFUS | Everything Added to Food in the United States |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| ERPG | emergency response planning guidelines |
| F | Fahrenheit |
| F1 | first-filial generation |
| FDA | Food and Drug Administration |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |

| | |
|---|---|
| FR | Federal Register |
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GGT | γ-glutamyl transferase |
| GRAS | generally recognized as safe |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| HHS | Department of Health and Human Services |
| HPLC | high-performance liquid chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Level of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| mCi | millicurie |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| MSHA | Mine Safety and Health Administration |
| Mt | metric ton |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NCEH | National Center for Environmental Health |
| ND | not detected |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |

| | |
|---|---|
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute for Occupational Safety and Health |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NTP | National Toxicology Program |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| PAC | Protective Action Criteria |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PEHSU | Pediatric Environmental Health Specialty Unit |
| PEL | permissible exposure limit |
| PEL-C | permissible exposure limit-ceiling value |
| PFBA | perfluorobutanoic acid |
| PFBS | Perfluorobutane sulfonic acid |
| PFDA | perfluorodecanoic acid |
| PFDoDA | perfluorododecanoic acid |
| PFHpA | perfluoroheptanoic acid |
| PFHxA | perfluorohexanoic acid |
| PFHxS | perfluorohexane sulfonic acid |
| PFNA | perfluorononanoic acid |
| PFOA | perfluorooctanoic acid |
| FOSA | perfluorooctane sulfonamide |
| PFOS | perfluorooctane sulfonic acid |
| PFUnA | perfluoroundecanoic acid |
| pg | picogram |
| PND | postnatal day |
| POD | point of departure |
| ppb | parts per billion |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure level/limit |
| REL-C | recommended exposure level-ceiling value |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SD | standard deviation |
| SE | standard error |
| SGOT | serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST) |
| SGPT | serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT) |
| SIC | standard industrial classification |

| | |
|---|---|
| SMR | standardized mortality ratio |
| sRBC | sheep red blood cell |
| STEL | short term exposure limit |
| $T_{1/2}$ | Half-life |
| TLV | threshold limit value |
| TLV-C | threshold limit value-ceiling value |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |
| USNRC | U.S. Nuclear Regulatory Commission |
| VOC | volatile organic compound |
| WBC | white blood cell |
| WHO | World Health Organization |

| | |
|---|---|
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| $q_1^*$ | cancer slope factor |
| – | negative |
| + | positive |
| (+) | weakly positive result |
| (–) | weakly negative result |