MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Perfluorooctanoic Acid (PFOA) (CAS No. 335-67-1)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Updated Derivation of Screening Level

DATE: April 25, 2024

The initial threshold screening level (ITSL) for perfluorooctanoic acid (PFOA) is 0.0001 µg/m³ with 24-hour averaging time.

This updated ITSL is based on a reference dose (RfD) for PFOA derived by the U.S. Environmental Protection Agency (EPA, 2024) Office of Water. EPA (2024) derived the RfD based on epidemiologic studies that showed immune (decreased anti-tetanus and anti-diphtheria antibody concentrations in children), developmental (decreased birth weight), and cardiovascular (increased total cholesterol) effects. The RfD is 3E-8 mg/kg/day.

The previous ITSL of 0.07 µg/m³ with 24-hour averaging time is being rescinded at this time (see attached memo).

Pursuant to Rule 232(1)(b) the ITSL is calculated as follows:

ITSL = RfD × (Default Body weight)/(Default Inhalation rate) × unit conversion
ITSL = 3E-8 mg/kg/day × 70kg/20m³ × 1000 µg/mg
ITSL = 0.000105 µg/m³, rounded to 1 significant figure as 0.0001 µg/m³

Because the developmental effects of PFOA can occur over short periods of time, pursuant to Rule 232(2)(d) the averaging time is 24 hours.

Additionally, the PFOA screening level note No. 37 is rescinded because EPA no longer recommends comparing the sum of the concentrations of PFOA and perfluorooctane sulfonic acid to the health-based exposure standard.

Reference

EPA, 2024. FINAL. Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOS) and Related Salts. U.S. Environmental Protection Agency. Office of Water (4304T). Health and Ecological Criteria Division. Washington, DC 20460. EPA Document No. 815R24006. https://www.epa.gov/system/files/documents/2024-04/main_final-toxicity-assessment-for-pfoa_2024-04-09-refs-formatted.pdf

Attachment
MD:lh

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 5, 2018

To: File for Perfluorooctanoic Acid (PFOA) (CAS No. 335-67-1)

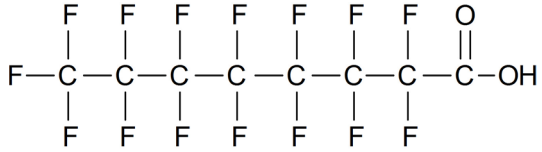
From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Derivation

The initial threshold screening level (ITSL) for perfluorooctanoic acid (PFOA) is 0.07 µg/m³ with 24-hour averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), ECHA (European Chemical Agency) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), EPA Acute Exposure Guideline Levels (AEGLs), National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs), U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTVs) for Superfund, International Agency for Research on Cancer (IARC) Monographs, California Office of Environmental Health Hazard Assessment (OEHHA), Chemical Abstract Service (CAS) - SciFinder (1967 – Nov. 2017), National Library of Medicine (NLM) Toxline, and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) for PFOA. EPA (2016) Office of Water derived an RfD of 0.00002 mg/kg/day (0.02 µg/kg/day) based on effects observed in a developmental toxicity study in mice. The molecular formula for PFOA is $C_8F_{15}O_2H$ and the molecular weight is 414.06g (see Figure 1 for structure).

Figure 1.
Molecular Structure of PFOA



The vapor pressure for PFOA is reported as 0.017 mmHg at 20°C (ATSDR, 2017). Typical ratios of indoor:outdoor perfluoroalkyl substances range from 50-400; thus 5-40 orders of magnitude greater concentrations indoors compared to outdoors (Fromme et al., 2009).

Occupational Exposure Level (OEL)

The ACGIH (2001) derived an 8-hour time weighted average (TWA) TLV of 0.01 mg/m³ for PFOA (including the ammonium salt). The TWA-TLV of 0.01 mg/m³ is based on data from the human oral exposure studies and the extended half-life in human blood, the no-observed-adverse-effect-levels found in rats exposed to ammonium perfluorooctanoate by various routes including inhalation, and the carcinogenic response (testicular Leydig cell tumors) following lifetime feeding of rats at 300 mg/kg. A potential ITSL could be derived from the OEL pursuant to Rule 232(1)(c) as:

Potential ITSL = (0.01 mg/m³)/(100) x 1000µg/mg
Potential ITSL = 0.1 µg/m³

Pursuant to Rule 232(2)(b), the OEL based ITSL would be given an eight-hour averaging time. However, the ACGIH (2001) did not clearly present data on how the TWA-TLV would be protective of occupational inhalation exposure concentrations, including what blood PFOA levels result from exposure concentrations, and relate those blood levels to the effects observed in animal and human toxicity studies. Because the derivation of the ACGIH TWA-TLV is ambiguous, it was deemed inappropriate to use the OEL to derive the ITSL for PFOA, especially since the derivation of the RfD by EPA (2016) appears to be of higher quality and would be health protective after converting the oral dose to inhalation dose (see below).

Inhalation Toxicity Information

Inhalation toxicity data in laboratory animals were limited to acute exposure, single and repeated exposures for pharmacokinetic studies, and a developmental toxicity study in rats. No subchronic or chronic inhalation toxicity studies in animals were available for assessment. Generally, adverse effects observed following inhalation exposure to PFOA were similar to effects following exposure to an irritating dust. For male rats exposed to PFOA as a dust in air, the 4-hour LC50 was 980 mg/m³ with adverse clinical signs of body weight loss, irregular breathing, red discharge around the nose and eyes, and corneal opacity and corrosion (Kennedy et al., 1986; 2004).

Hinderliter et al (2006) evaluated the relationship between inhalation exposures and plasma PFOA concentrations in male and female Crl:CD rats. In this study, groups of five rats per sex were exposed to 0, 1, 10, or 25 mg/m³ PFOA (nose only) for 6 hours/day, 5 days/week, for three weeks. Blood samples were taken and analyzed for PFOA before and immediately after exposure, three days per week for three weeks (study days 0, 2, 4, 7, 9, 11, 14, 16, 18). In female rats, PFOA was rapidly eliminated from the body, with little accumulation seen in the pre-exposure samples taken over the three-week exposure period. In male rats, levels of PFOA in the blood plasma accumulated over time. At the end of the exposure time, it appeared that the male rats in the two lowest dose groups had either reached or were close to steady state concentrations of PFOA in the plasma. In the highest dose group, the authors noted that plasma PFOA concentrations may not have reached steady state concentrations by the end of the exposure period given that the last sample taken had the highest PFOA plasma concentration (46 µg/mL). Steady state concentrations of 8, 21, and 36 µg/mL were reported for the male rats exposed to 1, 10, and 25 mg/m³ PFOA

which seems to contradict the author's previous statement that the high dose group did not reach steady-state plasma concentrations at the end of the exposure period. The authors stated that comparable steady state blood concentrations can be achieved by oral doses 0.3, 1, and 2 mg/kg in the rat. The source of the comparable oral exposure doses was not clear, and may be an unpublished study (i.e., Kemper, 2003) cited by the authors.

In an inhalation toxicity study, the embryo-fetal toxicity and teratogenic potential of ammonium perfluorooctanoate (APFO) was evaluated in two different experiments using Sprague Dawley rats (Staples et al., 1984). In the first experiment groups of 12 – 24 mated females were exposed to APFO (whole body) at concentrations of 0, 0.1, 1, 10, and 25 mg/m³ for 6 hours/day from days 6 -15 of gestation. Dams were sacrificed on day 21 of gestation and fetuses examined for abnormalities. In the second experiment, groups of 6 - 12 mated females were exposed to APFO at the same concentrations and in the same manner as in the first experiment, however in the second experiment, the dams were allowed to litter (Day 1, post-exposure), and then were sacrificed 22 days later on Day 23 post-exposure. Adverse clinical signs were observed in the dams of the two highest dose groups in both experiments, including wet abdomens (beginning in the perineal area), chromodacryorrhea, chromorhinorrhea, and an unkempt appearance. Additionally, in the highest dose group of Experiment I, three deaths occurred on days 12, 13, and 17 of gestation, and four dams surviving to day 21 of gestation became very lethargic. Liver weights were also significantly increased in the highest dose group. No teratogenic or adverse effects on reproductive performance were observed in any dose groups, however the fetal body weight (Experiment I) and the neonate body weight (Experiment II) in the highest dose group was significantly decreased from the control. This effect was no longer statistically significant by Day 4 post-exposure in Experiment II.

Cancer Effects Via Oral Exposure

The EPA Office of Water evaluated the cancer studies available for PFOA (EPA, 2016). The cancer effects of PFOA were investigated in rats (Butenhoff et al., 2012; Biegel et al, 2001). The two studies support a positive finding for the ability of PFOA to be weakly tumorigenic in one or more organs of male but not female rats. There are no carcinogenicity data from a second animal species. The study by Butenhoff et al. (2012) examined males and females; the Biegel et al. (2001) study only evaluated males. The elevated tumor types observed were:

- Liver (Butenhoff et al., 2012)
- Leydig Cell (Butenhoff et al., 2012; Biegel et al., 2001)
- Pancreatic Acinar Cell (Biegel et al., 2001)

The dose response information and tumor incidence data from the Butenhoff et al. (2012) and Biegel et al. (2001) study are summarized in Table 1, below. The data are limited in that only Butenhoff et al. (2012) tested more than one dose and only one tumor-type (Leydig Cell adenoma) demonstrated a dose-response relationship.

Table 1.
Summary of Tumor Data from Animal Studies

Tissue	Dietary Exposure Group (parts per million or ppm) 0	30	300	Tumor Type	Reference
Liver Male	7/50	2/50	10/50	Hepatocellular carcinoma	Butenhoff et al., 2012
Liver Male	0/80	NT	0/76	Hepatocellular carcinoma	Biegel et al., 2001
Liver Male	2/80	NT	10/76	Hepatocellular adenoma	Biegel et al., 2001
Liver Female	0/50	0/50	2/50	Hepatocellular carcinoma	Butenhoff et al., 2012
Testes Male	0/50	2/50	7/50	Leydig Cell adenomas	Butenhoff et al., 2012
Testes Male	0/80	NT	8/76	Leydig Cell adenomas	Biegel et al., 2001
Pancreas Male	1/80	NT	0/76	Acinar Cell carcinoma	Biegel et al., 2001
Pancreas Male	0/80	NT	7/76	Acinar Cell adenoma	Biegel et al., 2001

NT = not tested
(data adapted from EPA, 2016, Table 4-10, page 259)

Concerning the cancer dose-response assessment, EPA (2016) stated:

> The increase in hepatocellular tumors did not show a direct relationship to dose in male rats and was not significantly elevated in either males or females at the high dose when compared to controls. There was a dose-related significant increase in Leydig cell tumors in male rats in the Butenhoff et al. (2012) study which was confirmed by the high dose in the single dose mechanistic study by Biegel et al. (2001). At the high dose (300 ppm in the diet; 14.2 mg/kg/day) tumors were found in 14% of the male rats at the end of 2 years in the Butenhoff et al. (2012) study and 4% at the low dose (1.3 mg/kg/day). In the Biegel et al (2001) study 11% were affected at a dose of 300 ppm in the diet (13.6 mg/kg/day). In each case there were no Leydig cell tumors in the controls.

EPA (2016) concluded that PFOA is likely a non-linear carcinogen (i.e., “threshold”), meaning that the traditional carcinogenic risk assessment method of modeling tumor response using a linear extrapolation to zero dose-response may not be appropriate. To this end, EPA (2016) states:

> The data on a PPARα[1] -linked MOA[2] are strongest for the liver tumors. Some data also provide a link of PPARα to the Leydig cell and PACT[3] tumors observed in the rat 2-year bioassays. They are not as strong and identify a need for additional research justifying the suggestive evidence finding. However, when integrated with the metabolic inertness of PFOA in animals and humans, a linear response to dose is not likely. This is consistent with the tumor data. Thus, a nonlinear MOA is likely and the remaining challenge is to identify the critical event in each MOA that leads to development of the tumors.

Concerning the evidence for PFOA-induced cancer effects observed in human studies, EPA (2016) states:

[1] PPARα = Peroxisome proliferation activation receptor alpha
[2] MOA = mode of action for carcinogenic effects
[3] PACT = pancreatic acinar cell tumor

> The findings for cancer in humans provide support for an association between PFOA and kidney and testicular cancers; however, the number of independent studies examining each of these is limited. The support comes from high-exposure community studies examining cancer incidence and covering children and young adults (Barry et al. 2013; Vieira et al. 2013); there is some overlap in the cases included in these studies. The two occupational cohorts in Minnesota and West Virginia (most recently updated in Raleigh et al. 2014 and Steenland and Woskie 2012) do not support an increased risk of kidney or testicular cancer, but are limited by a very small number of observed cases. None of the general population studies examined these cancers, but associations were not seen in the general population studies addressing colorectal, breast, prostate, bladder, and liver cancer, with mean serum PFOA levels up to 0.0866 µg/mL (Bonefeld-Jørgensen et al. 2014; Eriksen et al. 2009; Hardell et al. 2014; Innes et al. 2014).

Beginning in 2006, nearly 70,000 community members in the Ohio River Valley whose drinking water had been contaminated by PFOA for decades were studied retrospectively by the C8 Panel (Frisbee et al., 2009; C8 Science Panel, 2012). EPA (2016) reviewed the findings of these coordinated research studies and reported:

> As part of the C8 Health Project, the C8 Science Panel (2012) concluded that a probable link existed between PFOA exposure and testicular and kidney cancer.
>
> A group of independent toxicologists and epidemiologists critically reviewed the epidemiological evidence for cancer based on 18 studies of occupational exposure to PFOA and general population exposure with or without coexposure to PFOS. The project was funded by 3M, but the company was not involved in the preparation or approval of the report. The authors evaluated the published studies based on the study design, subjects, exposure assessment, outcome assessment, control for confounding, and sources of bias. They followed the Bradford Hill guidelines on the strength of the association, consistency, plausibility, and biological gradient in reaching their conclusion. They found a lack of concordance between community exposures and occupational exposures one or two magnitudes higher than those for the general population. The discrepant findings across the study populations were described as likely due to chance, confounding, and/or bias (Chang et al. 2014).

Chang et al. (2014) found that, “Taken together, the epidemiologic evidence does not support the hypothesis of a causal association between PFOA or PFOS exposure and cancer in humans.”

Despite the finding that PFOA is a likely threshold carcinogen, EPA (2016) derived an oral cancer slope factor (CSF) for PFOA using non-threshold methodology based on the following rationale:

> Under the EPA 2005 cancer guidelines, the evidence for the carcinogenicity of PFOA is considered suggestive because only one species has been evaluated for lifetime exposures and the tumor responses occurred primarily in males. Dose-response data are only available for the LCTs [Leydig cell tumors] in one study. However, two studies involving members of the C8 Health Project showed a positive association between PFOA levels (mean at enrollment of 0.024 µg/mL) and kidney and testicular cancers (Barry et al. 2013; Vieira et al. 2013). Therefore, the data on LCTs from Butenhoff et al.

> (2012) were modeled to provide a perspective on the magnitude of the potential cancer risk as it compares with the level of protection provided by the RfD.
>
> The dose-response for the LCTs from Butenhoff et al. (2012) was modeled using EPA's Benchmark Dose Software (BMDS) Version 2.3.1. The multistage cancer model predicted the dose at which a 4% increase in tumor incidence would occur. The 4% was chosen as the low-end of the observed response range within the Butenhoff et al. (2012) results.

EPA (2016) goes on to derive an oral CSF of 0.07 $(mg/kg/day)^{-1}$ based on increased incidence of Leydig cell tumors reported by Butenhoff et al. (2012). However, given the equivocal carcinogenic effects produced by exposure to PFOA in animals and humans and a carcinogenic MOA assessment indicating that the animal tumors may be acting via a threshold mechanism (see PPARα discussion on page 4 above), EPA's decision to derive an oral CSF using a linear quantitation method (i.e., multistage cancer model) for carcinogenic risk seems inconsistent with a likely threshold MOA. EPA (2016) also states that the drinking water, "[G]uideline derived [from the RfD] from the developmental endpoint will be protective for the cancer endpoint." Because of the EPA (2016) findings regarding PFOA carcinogen risk assessment, and the apparent protectiveness of the RfD for cancer effects, it was deemed inappropriate for MDEQ-Air Quality Division to use the oral CSF to derive an inhalation unit risk.

Non-Cancer Effects

EPA derived an oral reference dose (RfD) of 0.00002 mg/kg based on adverse effects observed in a developmental toxicity study (EPA, 2016). Excerpts from EPA's review are quoted below:

> Human epidemiology data report associations between PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney). Epidemiology studies examined workers at PFOA production plants, a high-exposure community population near a production plant in the United States (i.e., the C8 cohort), and members of the general population in the United States, Europe, and Asia. These studies examined the relationship between serum PFOA concentration (or other measures of PFOA exposure) and various health outcomes. Exposures in the highly exposed C8 community are based on the concentrations in contaminated drinking water and serum measures. Exposures among the general population typically included multiple PFASs as indicated by serum measurements.
>
> Mean serum levels among the occupational cohorts ranged from approximately 1 to 4 micrograms per milliliter (µg/mL) and in the C8 cohort ranged from 0.01 to 0.10 µg/mL.
>
> Extensive data on humans and animals indicate ready absorption of PFOA and distribution of the chemical throughout the body by noncovalent binding to plasma proteins. Studies of postmortem human tissues identify its presence in liver, lung, kidney, and bone. PFOA is not readily eliminated from the human body as evidenced by the half-life of 2.3 years among members of the general population. In contrast, half-life values for the monkey, rat, and mouse are 20.8 days, 11.5 days, and 15.6 days, respectively.

Concerning the pharmacokinetics (PKs)(i.e., absorption, distribution, metabolism, elimination) of PFOA, EPA (2016) stated:

> In linking chemical exposure to toxic endpoints, careful consideration of PKs is crucial. This is especially true for PFOA, where inter-species and gender variation in CL[4] half-life can vary by several orders of magnitude. If the toxicological endpoints are assumed to be driven by internal concentrations, the internal exposure needs to be calculated and considered across species. Differences in PKs (e.g., male rats excrete PFOA more slowly than females) and differences across species produce differences in the external dose needed to achieve the same internal dose. The use of the animal data and the available PK model allows for the incorporation of species differences in saturable renal resorption, dosing duration, and serum measurements for doses administered to determine HEDs[5] based on average serum concentration and CL.

EPA's (2016) RfD for PFOA of 0.00002 mg/kg/day was based on effects observed in a developmental toxicity study in mice (Lau et al. 2006) where PFOA was given to pregnant mice at doses of 1, 3, 5, 10, 20, or 40 mg/kg by gavage once daily from gravid-day (GD) 1 through GD 17. All pregnancies were lost at the 40 mg/kg dose level. Significantly reduced ossification of sternebrae, caudal vertebrae, metacarpals, metatarsals, phalanges, calvaria, supraoccipital, and hyoid were observed in the 10 and 20 mg/kg dose groups (Lau et al. 2006). Visceral examination also revealed minor tail and limb defects and microcardia in these dose groups (Lau et al. 2006). See Table 2 for a description of the derivation of the RfD.

Table 2.
EPA's (2016) Derivation of the Oral Reference Dose (RfD) for PFOA

POD*	HED POD mg/kg/day	UFH	UFA	UFL	UFtotal	RfD
PK-HED$_{LOAEL}$ Lau et al. (2006). mice ↓ pup ossification (m, f), accelerated male puberty	0.0053	10	3	10	300	0.00002
PK-HED$_{LOAEL}$ Butenhoff et al. (2004). ↓ relative body weight/ ↑ relative kidney weight and ↑kidney:brain weight ratio in F0 and F1 at sacrifice	0.0064	10	3	10	300	0.00002

Data adapted from EPA (2016) Table 4-8, page 253.
*Notes: POD = point of departure. PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; m = male; f = female; UFH = intra-individual uncertainty factor; UFA = interspecies uncertainty factor; UFL = LOAEL to NOAEL uncertainty factor; UF-total = total (multiplied) uncertainty factor

[4] CL = clearance. (e.g., elimination)
[5] HEDs = human equivalent doses

EPA (2016) states:

> The RfD is based on reduced ossification and accelerated puberty (in males). The total uncertainty factor (UF) of 300 was applied to the human equivalent dose (HED) lowest-observed-adverse-effect-level (LOAEL) from Lau et al. (2006) and includes a UF of 10 for intra-human variability, an UF of 3 to account for toxicodynamic differences between animals and humans, and a UF of 10 to account for use of a LOAEL as the point of departure (POD).
>
> Decreased pup body weights also were observed in studies conducted in mice receiving external doses within the same order of magnitude (1, 3, and 5 mg/kg/day) as those chosen for the RfD. These studies, however, lacked serum levels and were not amenable to physiologically based pharmacokinetic modeling. Overall, the developmental and reproductive toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity. The selected RfD is supported by the other candidate RfDs (also 0.00002 mg/kg/day) based on effects on the immune system in a 15-day short-term study by DeWitt et al. (2008) and on the kidneys of F0 (parental animal) and F1 (progeny) males in a two-generation study of developmental and reproductive toxicity [Butenhoff et al. (2004)].

Although the key study performed by Lau et al., (2006) provided NOAELs of 1, 3 and 5 mg/kg/day doses, EPA (2016) used the HED derived from the LOAEL of 10 mg/kg/day and corresponding PFOA serum concentration to derive the RfD. EPA (2016) provided the following rationale for using the LOAEL dose level as the POD:

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

Derivation of the Initial Threshold Screening Level

An ITSL (analogous to an RfC) can be derived from an RfD if portal of entry effects (e.g., respiratory tract effects) are not expected at the toxicologically relevant dose-range, first pass[6] concerns, and systemic absorption via the lung is likely. PFOA is expected to be a particulate, is not known to be rapidly metabolized by the liver, and is readily absorbed via the inhalation pathway (Kennedy et al., 1986, Hinderliter et al., 2006). Pursuant to Rule 232(1)(b) the ITSL was calculated as follows:

> ITSL = RfD x (avg. body weight)/(inhalation rate per day) x unit-conversion
> ITSL = (0.00002 mg/kg) x (70kg)/(20m³) x 1000µg/mg
> ITSL = 0.07 µg/m³ with 24-hr averaging time

An alternative to the default route-to-route conversion should be based on chemical-specific route-to-route extrapolation, and is preferable to the default conversion used above. To this end, a study was identified by Hinderliter, et al., (2006) that looked at plasma concentrations of PFOA after both inhalation and oral dosing:

> [T]he pharmacokinetic properties of inhaled PFOA in male and female rats are similar to those observed in male and female rats following oral dosing with PFOA. It is thus possible to use this internal dose metric (plasma PFOA) for route-to-route dose extrapolation, with inhalation exposures of 1, 10, and 25 mg/m³ PFOA corresponding to oral doses of approximately 0.3, 1.0, and 2.0 mg/kg in rats.
>
> The same steady state blood levels of PFOA can be compared in male rats following oral doses of approximately 0.3, 1, and 2 mg/kg body weight. This approximates a 10-fold difference; i.e., it is predicted that a 1 mg/kg oral dose produces the same PFOA blood level as a 10 mg/m³ inhalation exposure in rats.

As Hinderliter et al., (2006) suggests, the ratio of 1 mg/kg oral dose to 10 mg/m³ inhalation dose (i.e., 10:1) could be used as a route-to-route adjustment factor (oral to inhalation) to obtain the same internal plasma dose. If the plasma dose is the appropriate dose metric to assess PFOA toxicity, the following route-to-route conversion can be made:

> Alternative ITSL = RfD mg/kg x Route Adjustment Factor x unit-conversion
> Alternative ITSL = (0.00002 mg/kg) x (10mg/m³)/(1mg/kg) x 1000µg/mg
> Alternative ITSL = 0.2 mg/m³

It appears from the data presented by Hinderliter et al., (2006) that inhalation dose to plasma concentration rate varies at different dose levels (see Table 2). Therefore, as a further refinement of route-to-route extrapolation, a regression analysis can be used to convert oral-to-inhalation at the lower inhalation dose levels, especially in the dose range of the RfD (see Figure 2).

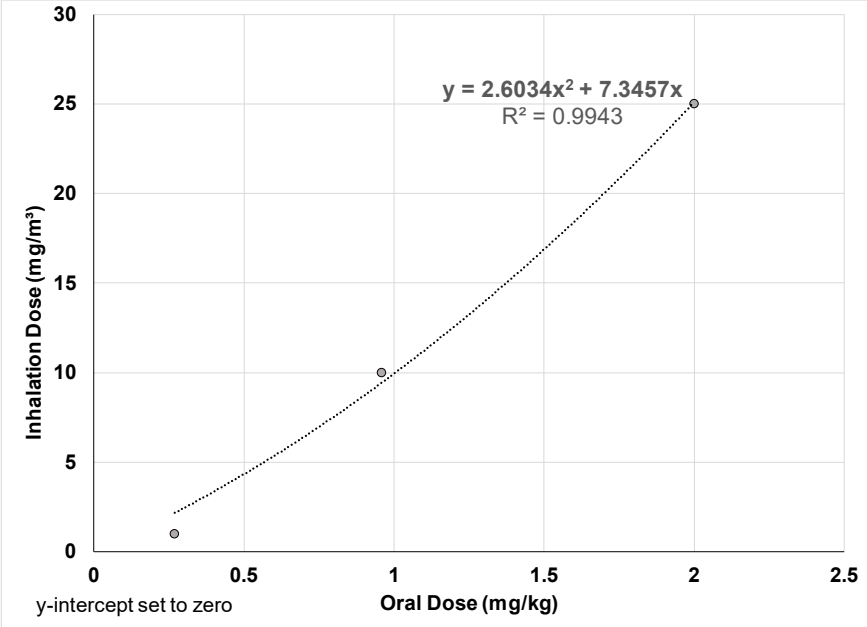
[6] The first pass effect (also known as first-pass metabolism or pre-systemic metabolism) is a phenomenon of chemical metabolism whereby the concentration of a chemical is greatly reduced before it reaches the systemic circulation. This first pass through the liver thus greatly reduces the bioavailability of the chemical via the systemic circulation.

Table 2.
Inhalation and Oral Doses Producing the Same Plasma Concentrations

Inhalation (mg/m³)	Oral (mg/kg)	Ratio
1	0.27	3.7
10	0.96	10.4
25	2.0	12.5

From Hinderliter et al., 2006

Figure 2.
Second Order Polynomial Trendline
for Oral Doses vs. Inhalation Doses



Data from Hinderliter et al., 2006

The RfC can be determined using the regression equation of 2nd order polynomial "trendline" (see Figure 2): $y=ax^2+bx+c$, with intercept set to 0.0 from Microsoft Excel[7]. Using the RfD as the independent variable "x" of 0.00002 mg/kg, and solving for the dependent variable "y," the RfC is calculated as:

$y = 2.603x^2 + 7.3457x$
$y = 2.6034(0.00002)^2 + 7.3457(0.00002)$
$y = 2.6034(4E\text{-}10) + 0.0001469$
$y = 1.04E\text{-}9 + 0.0001469$
$y = 1.469E\text{-}4$

With unit conversion of mg to µg (1 to 1000), the RfD of 0.00002 mg/kg equates to an alternative ITSL of 0.15 µg/m³ (rounded to 2 significant figures) using the Excel trendline equation derived from Hinderliter et al. (2006).

[7] Microsoft® Excel® 2016 MSO (16.0.8730.2046) 32-bit

A comparison of the three route-to-route conversion options used to derive an RfC from the RfD is shown in Table 3.

Table 3.
Comparison of RfCs Derived from RfD
Using Different Scaling Factors

Candidate RfC (µg/m³)	Method (scaling factor)
0.07	Default, Rule 232(1)(b) (70kg/20m³)
0.2	Hinderliter et al., 2006 (10 mg/m³ = 1 mg/kg)
0.15	Polynomial Trendline ($y = 2.603x^2 + 7.3457x$)

As mentioned above, the Hinderliter et al., (2006) report did not specifically present the data for the oral dose to internal blood plasma concentrations; however, it appears that Kemper and Jepson (2003) is referenced. Unfortunately, Kemper and Jepson (2003) is an unpublished report DuPont-7473. EPA (2016) references the same DuPont-7473 report, as Kemper, 2003 and provides detailed data tables describing the oral dose and various measures of plasma concentrations (e.g., max plasma concentration, etc.) Apparently, EPA (2016) used Kemper (2003) in the PK model development to relate rat plasma concentrations to those of humans in order to calculate the human equivalent dose (HED; see discussion on page 6 and Table 2 on page 7 above). Because EPA (2016) cited Kemper (2003) in the development of the RfD, it can be assumed that the date used to relate the oral dose to plasma concentration is reliable. However, there is still an unclear understanding of how Hinderliter et al. (2006) derived a relationship between oral dose and plasma concentration, and plasma concentration and inhalation dose. Therefore, the default method to calculate an ITSL using Rule 232(1)(b) of route to-route conversion was used (i.e., ITSL = RfD x 70kg/20m³), resulting in a final ITSL of 0.07 µg/m³.

The ITSL averaging time of 24-hr is appropriate because the ITSL of 0.07 µg/m³ is based on a short-term developmental toxicity study and acute adverse effects: reduced ossification and accelerated puberty in male mice.

If PFOA and perfluorooctanoic sulfonate (PFOS, CAS No. 1763-23-1) are co-emitted, then the proposed emission rates should be evaluated together, such that the impacts of PFOA and PFOS combined shall be less than or equal to 0.07 µg/m³ with a 24-hr averaging time, for Rule 225 applicability.

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