Health Based Guidance for Air
Environmental Impacts Analysis Unit, Environmental Health Division
651-201-4899

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Air Toxicological Summary for: Perfluorohexanoic acid (PFHxA)

CAS: 307-24-4
Synonyms: PFHxA, Perfluorohexanoate

Air Exposure Durations:
Acute - dosing duration 24-hours or less
Short-term - repeated dosing for more than 24-hours, up to approximately 30 days
Subchronic - repeated dosing for more than 30 days, up to approximately 8 years (10 percent of a lifespan in humans; more than 30 days up to approximately 90 days in typical laboratory rodent species)
Chronic = repeated dosing for more than approximately 8 years (10 percent of a life span in humans; more than approximately 90 days in typical laboratory rodent species)

Acute Non-Cancer Risk Assessment Advice (RAA_{Acute}) = Not Derived (Insufficient Data)

Non-Cancer Short-term RAA ($RAA_{Short\text{-}term}$) = 1 µg/m^3

= Reference Dose (mg/kg-d) x Route-to-route scaling factor (kg/m^3-d) x (1000 µg/mg)

= 0.00032 (mg/kg-d) x (70 kg/20 m^3-d) x (1000 µg/mg)

= 1.12 µg/m^3 = 1 µg/m^3

Reference Dose/Concentration:	HED/Total UF = 0.0958/300 = 0.00032 mg/kg-d (laboratory animal – SD rats)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	25.9 mg/kg-d (administered dose $BMDL_{1SD}$, NTP 2019)
Dose Adjustment Factor (DAF):	Chemical and Study-Specific Toxicokinetic Adjustment Half-life$_{MaleRat}$/Half-life$_{Human}$ = 2.87 hrs/768 hrs = 0.0037 (based on Dzierlenga et al 2020, for male rats, and Russell et al 2013, for humans)
Human Equivalent Dose (HED):	POD/DAF = 25.9 mg/kg-d x 0.0037 = 0.0958 mg/kg-d

Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (e.g., lack of a 2-generation study, lack of thyroid hormone measurements or neurodevelopmental toxicity in young offspring in a development/reproductive study, and lack of immunotoxicity studies as well as evidence of pup body weight effects near the selected POD)
Critical effect:	Decreased total T4
Co-critical effects:	Decreased pup body weight
Additivity endpoints:	Developmental, Thyroid

Non-Cancer Subchronic RAA ($RAA_{Subchronic}$) = 0.5 µg/m^3

= Reference Dose (mg/kg-d) x Route-to-route scaling factor (kg/m^3-d) x (1000 µg/mg)

= 0.00015 (mg/kg-d) x (70 kg/20 m^3-d) x (1000 µg/mg)

= 0.525 µg/m^3 rounded to 0.5 µg/m^3

Reference Dose/Concentration:	HED/Total UF = 0.045/300 = 0.00015 mg/kg-d (laboratory animal – SD rats)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	22.5 mg/kg-d (administered dose $BMDL_{10\%}$, Loveless et al 2009)
Dose Adjustment Factor (DAF):	Chemical and Study-Specific Toxicokinetic Adjustment Half-life$_{MaleRat}$/Half-life$_{Human}$ = 1.5 hrs/768 hrs = 0.0020 (based on Gannon et al 2011, for male rats, and Russell et al 2013, for humans)
Human Equivalent Dose (HED):	POD/DAF = 22.5 mg/kg-d x 0.0020 = 0.045 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (assessment of thyroid effects was compromised by missing serum hormone data. A multigeneration reproductive study has not been conducted, however the database does include an extended one generation developmental study)
Critical effects:	Nasal epithelium degeneration
Co-critical effects:	Decreased bilirubin
Additivity endpoints:	Hepatic (liver) system, Respiratory system

Non-Cancer Chronic RAA ($RAA_{Chronic}$) = 0.5 µg/m^3

= Reference Dose (mg/kg-d) x Route-to-route scaling factor (kg/m^3-d) x (1000 µg/mg)

= 0.00015* (mg/kg-d) x (70 kg/20 m^3-d) x (1000 µg/mg)

= 0.525 µg/m^3 rounded to 0.5 µg/m^3

*Reference Dose: Per MDH 2021, the calculated Chronic RfD was higher in magnitude than the Subchronic RfD. Therefore, the Chronic RfD is set to the Subchronic RfD, see study information above for details on the RfD derivation.

Further detail regarding the MDH 2021 PFHxA RfD can be found in the Toxicological Summary for Perfluorohexanoate.

Cancer Risk Assessment Advice = Not Applicable

Cancer classification:	Not classified
Inhalation Unit Risk (IUR):	Not applicable
Source of IUR:	Not applicable
Tumor site(s):	Not applicable

Volatile: No

Summary of Guidance Value History: There are no previous PFHxA air guidance values.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	Yes	No	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	--[2]	Yes[3]	Yes[4]	Yes[5]	Yes[6]

Comments on extent of testing or effects:

[1] MDH 2021; A significant positive correlation between PFHxA exposure and TGAb (thyroglobin antibodies) and TMAb (thyroid microsomal antibody) was reported in an epidemiological study. Short-term studies in adult laboratory animals identified decreased serum thyroid hormone levels. These effects form the basis of the short-term RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of thyroid evaluations in developing animals. Thyroid cellular hypertrophy in adult animals was also reported, but at doses ~3,000-fold higher than the subchronic/chronic RfD.

[2] MDH 2021; No immunotoxicity studies have been conducted. Three general toxicity studies reported decreased thymus weight at dose levels >5800-fold higher than the subchronic/chronic RfD. At slightly higher dose levels atrophy and necrosis in spleen and thymus as well as a depletion of lymph nodes were observed.

[3] MDH 2021; Decreases in pup body weight and increased pup mortality have been reported. These effects were observed at levels ~1500-fold higher than the subchronic/chronic RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of a two-generation study.

[4] MDH 2021; Significant decreases in maternal body weight gain during gestation and complete litter loss were reported at doses >3,000-fold higher than the subchronic/chronic RfD. Decreases in sperm count and seminiferous tubule spermatid retention were reported at doses 25,000-fold higher than the Subchronic/Chronic RfD.

[5] MDH 2021; Acute studies reported ataxia and abnormal gait at dose levels ~1,000-fold higher than the subchronic/chronic RfD. No neurological changes, based on functional observation battery and locomotor activity evaluations, were reported in adult rats following 90 days of exposure at levels up to ~5,000-fold higher than the subchronic/chronic RfD.

[6] Significant degeneration/atrophy to nasal olfactory epithelium at greater than 100 mg/kg/d and respiratory metaplasia at 500 mg/kg/day in rat gavage subchronic exposures. This effect, in part, formed that basis of the subchronic/chronic RfDs and occurred at orders of magnitude higher than the subchronic/chronic RfD.

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