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

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Air Toxicological Summary for: Perfluorohexanesulfonic acid (PFHxS)

CAS: 355-46-4
Synonyms: Perfluorohexane sulfonate, PFHxS

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, Subchronic, Chronic RAA ($RAA_{Short\text{-}term,\ Subchronic,\ Chronic}$) = 0.034 µg/m^3*

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

= 0.0000097 (mg/kg-d) x (70 kg/20 m^3-d) x (1000 µg/mg)

= 0.034 µg/m^3

Reference Dose/Concentration:	HED/Total UF = 0.00292/300 = 0.0000097 mg/kg-d (or 9.7 ng/kg-d) (adult Sprague Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	32.4 µg/mL (or mg/L) serum concentration (male rats - NTP 2018, MDH modeled $BMDL_{20\%}$)

Dose Adjustment Factor (DAF):	Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.25 L/kg x (0.693/1935 days) = 0.000090 L/kg-day. (Half-life from Li et al 2018)
Human Equivalent Dose (HED):	POD x DAF = 32.4 mg/L x 0.000090 L/kg-d = 0.00292 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 to address concerns regarding early life sensitivity to decreased thyroxine (T4) levels as well as lack of 2-generation or immunotoxicity studies
Critical effect:	decreased free T4
Co-critical effects:	decreased free and total T4, triiodothyronine (T3), and changes in cholesterol levels and increased hepatic focal necrosis
Additivity endpoints:	Hepatic (Liver) system, and Thyroid

*MDH 2020; Due to the highly bioaccumulative nature of PFHxS within the human body, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV is not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. In addition, accumulated maternal PFHxS is transferred to offspring (i.e., placental and breastmilk transfer). A single HBV has therefore been recommended for short-term, subchronic, and chronic durations. The HBV was derived using a toxicokinetic (TK) model previously developed by MDH (Goeden 2019). Further detail regarding the MDH 2020 PFHxS RfD can be found in the Toxicological Summary for Perfluorohexane sulfonate (https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf).

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 PFHxS 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-limited
Effects observed?	Yes[1]	--[2]	No[3]	Yes[4]	No[5]	No[6]

Comments on extent of testing or effects:

[1]MDH 2020; Several human epidemiological studies have evaluated the possible association between serum PFHxS and alterations in thyroid hormone levels. Two studies found an association in women between serum PFHxS and thyroid hormone levels, however, other studies did not find this association. Two general population epidemiology studies have evaluated associations between PFHxS and reproductive hormones, finding no association.

Based on studies in laboratory animals, alterations in serum thyroid hormone levels, in particular thyroxine (T4), appear to be a sensitive effect. The POD is based on decreased serum T4 levels in adult male rats however, decreased serum T4 levels have also been reported in pregnant and lactating rats and pups. Unfortunately, serum PFHxS levels were not measured in pregnant or lactating rats or pups at the NOAEL and LOAEL dose levels, however, study results suggest that pups may be more sensitive than adult nonpregnant animals. A database uncertainty factor (DB UF) has been incorporated into the RfD derivation, in part, due to concerns that early life stages may be more sensitive.

Androgenic effects have also been evaluated in laboratory animals to a limited extent. No changes in adult male reproductive organ weights or sperm parameters were observed at serum levels up to ~600-fold higher than the 'reference' serum concentration. Androgenic activity was also evaluated in pups exposed in utero and through lactation. No significant effects were observed on anogenital distance, nipple retention, or reproductive organ weights at serum levels ~1300-fold higher than the 'reference' serum concentration.

[2]MDH 2020; Several epidemiology studies have examined the potential association between PFHxS and suppression of the immune system. Inverse or no associations were observed in these studies. In general, available studies have not found an association between PFHxS and infectious disease resistance or with hypersensitivity outcomes.

Immunotoxicity has not been studied in laboratory animals. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[3]MDH 2020; General population epidemiology studies have evaluated potential associations between maternal PFHxS and a variety of birth outcomes. A couple of studies have reported associations with birth weight or neurobehavioral outcome but others found no association.

Reproductive/developmental screening studies in rats and mice have not found treatment related changes in development outcome, including neurobehavioral effects, at serum levels > ~900-fold higher than the 'reference' serum concentration. Neurobehavioral outcomes were also evaluated in a study using a single oral exposure to neonatal mice on postnatal day 10. No serum levels were measured and therefore, the results could not be quantitatively incorporated into MDH's assessment. No 2-generation study has been conducted. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[4]MDH 2020; In general, epidemiology studies evaluating potential associations between PFHxS and reproductive measures have not found any associations. A small number of studies have reported associations with earlier menopause or time to pregnancy. However, since menstruation, childbirth, and lactation are potential elimination routes for women this could confound the associations.

Laboratory studies in rats did not find changes in reproductive parameters at serum levels > ~1600-fold higher than the 'reference' serum concentration. A decrease in the number of pups per litter has been reported in mice, however the dose-response curve was flat and there was no difference in the number of pups born to the implant ratio. The 'reference' serum concentration is ~500-fold lower than the serum concentrations at which this effect occurs in mice, therefore the RfD is protective for this potential effect.

[5]MDH 2020; Two epidemiology studies have evaluated association between PFHxS serum levels and self-reported memory loss or periods of confusion. One study reported a decrease in risk at the fifth quintile whereas the second study found no association.

Laboratory animal studies have evaluated neurotoxicity using the functional observation battery (FOB) and motor activity assessment. No effects were observed on adult rats and mice at serum concentrations >~600-fold higher than the 'reference' serum concentration. Potential neurological effects have also been evaluated in rat pups using these same evaluation tools. No effects were observed at serum concentrations up to ~800-fold higher than the 'reference' serum concentration. A neurotoxicity evaluation following a single oral dose to neonatal animals has also been conducted. See footnote #3 above.

[6]Oral studies in laboratory animals have not found consistent evidence of histological alterations for PFHxS exposure. Two studies that examined the respiratory tract of rats administered ≤10 mg/kg/day PFHxS or mice administered ≤3 mg/kg/day by gavage in a reproductive study (40–60 days of dosing) showed no treatment-related effects. No human respiratory related studies of PFHxS were found.

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