Health-Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

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Toxicological Summary for: Perfluorohexanoate

CAS: **92612-52-7 (anion)**
307-24-4 (free acid)
21615-47-4 (ammonium salt)
2923-26-4 (sodium salt)

Synonyms: PFHxA; Perfluorohexanoic acid

Acute Non-Cancer Health-Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 0.2 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00032 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 0.22 rounded to **0.2 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA, 2000) to select appropriate RSCs. For PFHxA, an RSC of 0.2 was used for all exposure durations due to concerns about infant exposures from house dust and diet, potential exposures from the breakdown of precursor chemicals, and uncertainty about infant exposure levels.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

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 $Half\text{-}life_{MaleRat}/Half\text{-}life_{Human}$ = 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 x 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(s):	Decreased total T4
Co-critical effect(s):	Decreased pup body weight
Additivity endpoint(s):	Developmental, Thyroid [E]

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 0.2 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00015 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 0.405 rounded to 0.4 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

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 $\text{Half-life}_{MaleRat}/\text{Half-life}_{Human}$ = 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 x 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 (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(s):	Nasal epithelium degeneration
Co-critical effect(s):	Decreased bilirubin
Additivity endpoint(s):	Hepatic (liver) system, Respiratory system

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 0.2 µg/L. Additivity endpoints: Developmental, Thyroid [E]

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 0.2 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00015 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 0.67 rounded to 0.7 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

***Reference Dose/Concentration: The calculated Chronic RfD was higher in magnitude than the Subchronic RfD. Therefore, the Chronic RfD is set to the Subchronic RfD, see information above for details on the RfD derivation.

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 0.2 µg/L. Additivity endpoints: Developmental, Thyroid [E]

Cancer Health-Based Value (cHBV) = Not Applicable

Volatile: Nonvolatile

Summary of Guidance Value History:
There are no previous guidance values for PFHxA. The 2021 derived values represent new guidance.

Additional Information on the MDH TK model (Goeden et al., 2019):
PFHxA water guidance was calculated using MDH's standard equations shown above. The Goeden et al. (2019) toxicokinetic model previously used to calculate guidance for PFOA, PFOS, and PFHxS was evaluated during this review because PFHxA crosses the placenta and is found in breastmilk. The toxicokinetic data that the model requires are quite limited for PFHxA (e.g., no information on breastmilk:maternal serum ratio, limited information on half-life). As a result, the model was not used quantitatively to derive PFHxA water guidance. However, the PFHxA modelling results, using the best available information for model parameters, indicate that water guidance of 0.2 µg/L developed using the standard equation is adequately protective.

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
Tested for specific effect?	Yes	No	Yes	Yes	Yes

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects observed?	Yes[1]	-[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]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] 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]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] 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] 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.

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