Toxicological Summary for: Perfluorobutyrate

CAS: 375-22-4
Synonyms: Perfluorobutanoic Acid (PFBA), Perfluorobutyric acid, Heptafluorobutyric acid

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

* While a developmental study is available for PFBA, a human equivalent dose (HED) forms the basis of the reference dose and assumes steady state conditions that cannot be achieved from a one-day exposure. Based on a mean human half-life of 3 days steady-state conditions would be established within ~ 9-15 days. At the present time the information necessary to estimate less than steady-state doses is not available. The short-term HRL assessment incorporated information regarding developmental effects.

Short-term Non-Cancer Health Based Value (nHBV_{short-term}) = 7 \mu g/L

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
\[
= (0.0038 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ \mu g/mg})
\]
\[
= 6.67 \text{ rounded to } 7 \mu g/L
\]

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81
Critical effect(s): Decreased cholesterol
Co-critical effect(s): Increased relative thyroid weight, decreased serum total thyroxine (TT4), decreased dialysis free thyroxine (dFT4)
Additivity endpoint(s): Hepatic (liver) system, Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{subchronic}$) = $nHBV_{short-term} = 7 \mu g/L$

\[
(\text{Reference Dose, mg/kg-d)} \times (\text{Relative Source Contribution)} \times (\text{Conversion Factor}) \times (\text{Subchronic Intake Rate, L/kg-d})
\]

\[
= (0.0029 \text{ mg/kg-d)} \times (0.2)^* \times (1000 \text{ \mu g/mg})
(0.070 \text{ L/kg-d})^{**}
\]

\[
= 8.29 \text{ rounded to } 8 \mu g/L
\]

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 0.86/300 = 0.0029 mg/kg-d (rat)
Source of toxicity value: Determined by MDH in 2008
Point of Departure (POD): 6.9 mg/kg-d (NOAEL, NOTOX 2007b)
Dose Adjustment Factor (DAF): Chemical-Specific Toxicokinetic Adjustment ($t^{1/2}_{Human} / t^{1/2}_{MaleRat} = 72 \text{ hours} / 9.22 \text{ hours} = 8$) ($t^{1/2}$ based on Chang et al. 2008, Olsen et al. 2007b)
Human Equivalent Dose (HED): POD/DAF = 6.9 mg/kg-d / 8 = 0.86 mg/kg-d (chemical specific basis)
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 effect(s): Liver weight changes, morphological changes in liver and thyroid gland, decreased TT4, decreased red blood cells, decreased hematocrit and hemoglobin
Co-critical effect(s): Increased relative thyroid weight, decreased serum TT4 and dFT4, decreased cholesterol, delayed eye opening
Additivity endpoint(s): Developmental, Hematological (blood) system, Hepatic (liver) system, Thyroid (E)
The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Additivity endpoints: Hepatic (liver) system, Thyroid (E)

Chronic Non-Cancer Health Based Value (nHBV\textsubscript{Chronic}) = nHBV\textsubscript{Short-term} = 7 µg/L

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
(\text{Chronic Intake Rate, L/kg-d})
\]

\[
= (0.0029 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg}) \\
(0.044 \text{ L/kg-d})^{**}
\]

= 13.2 rounded to 10 µg/L

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 0.86/300 = 0.0029 mg/kg-d (rat)
Source of toxicity value: Determined by MDH in 2008
Point of Departure (POD): 6.9 mg/kg-d (NOAEL, NOTOX 2007b)
Dose Adjustment Factor (DAF): Chemical-Specific Toxicokinetic Adjustment (t½\textsubscript{Human} / t½\textsubscript{Male RAT} = 72 hours / 9.22 hours = 8) (t½ based on Chang et al. 2008, Olsen et al. 2007b)
Human Equivalent Dose (HED): POD/DAF = 6.9 mg/kg-d / 8 = 0.86 mg/kg-d (chemical specific basis)
Total uncertainty factor (UF): 300
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for interspecies 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 effect(s): Liver weight changes, morphological changes in liver and thyroid gland, decreased TT4, decreased red blood cells, decreased hematocrit and hemoglobin

Co-critical effect(s): Increased relative thyroid weight, decreased serum TT4 and dFT4, decreased cholesterol, delayed eye opening

Additivity endpoint(s): Developmental, Hematological (blood) system, Hepatic (liver) system, Thyroid (E)

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Additivity endpoints: Hepatic (liver) system, Thyroid (E)

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Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification: Not Classified
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:
MDH promulgated short-term, subchronic and chronic Health Risk Limits (nHRL) of 7 μg/L in 2011. In 2017, MDH re-evaluated the noncancer HRLs. The values did not change as a result of the evaluation and incorporation of MDH’s most recent risk assessment methodology.

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.

<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects observed?</td>
<td>Yes¹</td>
<td>No</td>
<td>Yes²</td>
<td>No</td>
<td>No³</td>
</tr>
</tbody>
</table>

Comments on extent of testing or effects:

¹ Secondary observations, including decreased T4 levels, altered hyperplasia/hypertrophy of the follicular epithelium of the thyroid, and increased thyroid weight were noted in the 28 and 90 day studies. These effects are identified as critical or co-critical effects for the short-term, subchronic, and chronic duration HBVs.

² Developmental delays were observed in offspring of mice exposed during pregnancy. This effect was observed at 2-fold higher than the human equivalent dose, upon which the short-term RfD is based. Developmental effects are identified as secondary effects.

³ No available neurotoxicity studies. Secondary observations reported in the 28 and 90-day studies include delayed bilateral pupillary reflex for males exposed to a dose > 10-fold higher than the BMDL used as the basis of the short-term, subchronic, and chronic HBVs. Histopathological assessment of neuronal tissues (including the optic nerve) and motor activity evaluations did not reveal any treatment-related abnormalities.
Resources Consulted During Review:


Butenhoff, JL. 2007a. E-mail correspondence conveying benchmark dose calculations conducted by 3M for liver weight and cholesterol – 28 day PFBA study. February 6, 2007.

Butenhoff, JL. 2007b. Memorandum to Helen Goeden. October 9, 2007. Subject: Data Summary for mechanistic investigation results from samples for NOTOX study no. 470677.

Butenhoff, JL. 2007c. E-mail correspondence conveying BMD estimates from Dr. Gaylor. Attachments: Benchmark Dose Calculations for Ammonium Perfluorobutyrate (PFBA) and Benchmark Dose Calculations for Ammonium Perfluorobutyrate (PFBA) based on Thyroid Hypertrophy/Hyperplasia by Dr. David W. Gaylor, Gaylor and Associates, LLC. December 13, 2007.


Butenhoff, JL. 2008b. E-mail correspondence conveying the final data summary for the thyroid hormone and thyrotropin analyses and Quantitative RT-PCR. Feb. 12, 2008


Mariash, C. 2008. Response to review questions posed by MDH regarding thyroid effects of PFBA.


NOTOX 2008b. Morphometric analyses on thyroids form male rats treated with MTDID-8391 under NOTOX Project 484492 (Repeated dose 90-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 3-week recovery period). November 20, 2008.


Olsen GW, ME Ellefson, DC Madsen, BA Gibson and CA Ley. 2007c. Protocol EPI-0031. A Biomonitoring Assessment of Perfluorobutyrate (PFBA) and Perfluorobutanesulfonate (PFBS) for Employees of the Chemical Perfluorobutyrate (PFBA) - Page 7 of 8


Rodricks, JV. 2007. Letter to Mr. John Stine with attached copy of ENVIROn’s drinking water health advisory (DWHA).


Weiss, JM, PL Andersson, MH lamoree, Peg Leonards, SPJ van Leeuwen, T Hamers. 2009. Competitive binding of poly- and perfluorinated compounds to the thyroid hormone transport protein transthyretin. Tox Cci 109(2)206-216.


Zoeller, RT. 2008. Response to review questions posed by MDH regarding thyroid effects of PFBA.