

Adopted as Rule: August 2018

Toxicological Summary for: Perfluorobutanoate

CAS: 45048-62-2 (anion)

375-22-4 (acid)

Synonyms: PFBA, Perfluorobutanoic Acid, Perfluorobutyric acid, Heptafluorobutyric acid

Acute Non-Cancer Health Risk Limit (nHRL_{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 Risk Limit (nHRL_{Short-term}) = 7 µg/L

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

$$= \frac{(0.0038 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.285 \text{ L/kg-d})^{**}}$$

$$= 6.67 \text{ rounded to } 7 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**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 = 0.38/100 = 0.0038 mg/kg-d (rat)
Source of toxicity value:	Determined by MDH in 2008
Point of Departure (POD):	3.01 mg/kg-d (BMDL _{1SD} , calculated by Butenhoff, 2007; based on NOTOX 2007a)
Dose Adjustment Factor (DAF):	Chemical-Specific Toxicokinetic Adjustment ($t_{1/2\text{Human}} / t_{1/2\text{MaleRat}} = 72 \text{ hours} / 9.22 \text{ hours} = 8$) ($t_{1/2}$ based on Chang et al. 2008, Olsen et al. 2007b)
Human Equivalent Dose (HED):	POD/DAF = 3.01 mg/kg-d / 8 = 0.38 mg/kg-d (chemical specific basis)
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty

(study did not identify a NOAEL or acceptable BMDL₁₀ for thyroid effects. A multigeneration reproductive study has not been conducted, however the database does include an extended one generation developmental study)

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 Risk Limit (nHRL_{Subchronic}) = nHRL_{Short-term} = 7 µg/L

$$\begin{aligned} & \frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic Intake Rate, L/kg-d})} \\ &= \frac{(0.0029 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.070 \text{ L/kg-d})^{**}} \\ &= 8.29 \text{ rounded to } 8 \text{ µg/L} \end{aligned}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**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 ($t_{1/2\text{Human}} / t_{1/2\text{MaleRat}} = 72 \text{ hours} / 9.22 \text{ hours} = 8$) ($t_{1/2}$ 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 nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 7 µg/L. Additivity endpoints: Hepatic (liver) system, Thyroid (E)

Chronic Non-Cancer Health Risk Limit (nHRL_{Chronic}) = nHRL_{Short-term} = 7 µg/L

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

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

$$= 13.2 \text{ rounded to } 10 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**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 ($t_{1/2\text{Human}} / t_{1/2\text{MaleRat}} = 72 \text{ hours} / 9.22 \text{ hours} = 8$) ($t_{1/2}$ 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 Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of

7 µg/L. Additivity endpoints: Hepatic (liver) system, Thyroid (E)

Cancer Health Risk Limit (cHRL) = 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. This guidance was adopted as HRLs in 2018.

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	No	Yes
Effects observed?	Yes ¹	-	Yes ²	-	No ³

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:

3M Cordova Electronic Materials Factory Employees. Final Report. Medical Department, 3M Company. July 30, 2007.

3M 2009a. ST-229 Final Report. 2009. Urinary Iodine Excretion Study in Rats (ToxDocs Study Number 08-048, MTDID 8391).

3M 2009b. 08-049 Final Report. 2009. 8-Day Repeat Dose Oral Toxicity Study of MTDID 8391 in Rats.

3M 2009c. ToxDocs 06-399: ADME Study of MTDID 8391 in Rats. Final report. May 28, 2009

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. 2008a. E-mail correspondence conveying PK analysis and preliminary risk assessment for PFBA from Drs. Harvey Clewell and Cecilia Tan of the Hamner Institutes for Health Sciences. Feb. 1, 2008.

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

Butenhoff, J., JA Bjork, SH Chang, DJ Ehresman, GA Parker, K Das, C Lau, PH Lieder, FM van Otterdijk, KB Wallace. 2012. Toxicological evaluation of ammonium perfluorobutyrate in rats: Twentyeight- day and ninety-day oral gavage studies. *Reproductive Toxicology*, 33, 513-530.

Chen YM and LH Guo. 2009. Fluorescence study on site-specific binding of perfluoroalkyl acids to human serum albumin. *Arch Toxicol*. Advanced access doi:10.1007/s00204-008-0359-x.

Chang, SC, JA Hart, DJ Ehresman, K Das, CS Lau, PE Noker, GS Gorman, YM Tan, JL Butenhoff. 2007. Poster Presentation at the annual Society of Toxicology meeting. Comparative Pharmacokinetics of Perfluorobutyrate (PFBA) in Rats, Mice, and Monkeys. *The Toxicologist*, Supplement to Toxicological Sciences. Vol 96(1) March 2007. Abstract 937.

- Chang, SC, K Das, DJ Ehresman, ME Ellefson, GS Gorman, JA Hart, PE Noker, YM Tan, PH Lieder, C Lau, GW Olsen, JL Butenhoff. 2008. Comparative Pharmacokinetics of Perfluorobutyrate (PFBA) in Rats, Mice, Monkeys, and Humans and Relevance to Human Exposure via Drinking Water. *Tox Sci* 104(1)40-53.
- Das KP, B Grey, J Butenhoff, S Tanaka, D Ehresman, D Zehr, C Wood and C Lau. 2007. Poster Presentation at the annual Society of Toxicology meeting. Effects of Perfluorobutyrate Exposure in Mice During Pregnancy. Vol 96(1) March 2007.
- Das, KP, BE Grey, RD Zehr, CR Wood, JL Butenhoff, SC Chang, DJ Ehresman, YM Tan, C Lau. 2008. Effects of perfluorobutyrate exposure during pregnancy in the mouse. *Tox Sci* 105(1)173-181.
- Ehresman DJ, SC Chang, JA Hart, WK Reagen, JL Butenhoff. 2007. Comparative Pharmacokinetics of Branched and Linear Perfluorobutyrate in Rats. Poster Presentation at International Congress of Toxicology XI Meeting. July 15-19, 2007. Montreal, Canada.
- Foreman, JE, SC Chang, DJ Ehresman, JL Butenhoff, CR Anderson, PS Palkar, BH Kang, FJ Gonzalez, JM Peters. 2009. Differential Hepatic Effects of Perfluorobutyrate Mediated by Mouse and Human PPAR α . *Tox Sci* 110(1)204-211.
- Hickey NJ, D Crump, SP Jones, SW Kennedy. 2009. Effects of eighteen perfluoroalkyl compounds (PFAs) on mRNA expression in chick embryo hepatocyte cultures. *Tox Sci*. Advance Access. July 17, 2009
- Ikeda T, K Aiba, K Fukuda, and M Tanaka. 1985. The Induction of Peroxisome Proliferation in Rat Liver by Perfluorinated Fatty Acids, Metabolically Inert Derivative of Fatty Acids. *J Biochem* 98:475-482.
- Interstate Technology and Regulatory Council (ITRC). 2017. Naming Conventions and Physical and Chemical Properties of Per- and Polyfluoroalkyl Substances (PFAS). http://pfas-1.itrcweb.org/wp-content/uploads/2017/10/pfas_fact_sheet_naming_conventions_11_13_17.pdf. Accessed February 6, 2018.
- Just WW, K Gorgas, FU Hartl, P Heinemann, M Salzer and H Schimassek. 1989. Biochemical Effects and Zonal Heterogeneity of Peroxisome Proliferation Induced by Perfluorocarboxylic Acids in Rat Liver. *Hepatology* 9(4):570-581.
- Kadar, H., B Veyrand, A Barbarossa, G Pagliuca, A Legrand, C Boshier, CY Boquien, S Durand, F Monteau, FP Antignac, R Le Bizec,. 2011. Development of an analytical strategy based on liquid chromatography-high resolution mass spectrometry for measuring perfluorinated compounds in human breast milk: Application to the generation of preliminary data regarding perinatal exposure in France. *Chemosphere*, 85, 473-480.

- Kozuka H, J Yamada, S Horie, T Watanabe, T Suga, and T Ikeda. 1991. Characteristics of Induction of Peroxisomal Fatty Acid Oxidation-Related Enzymes in Rat Liver by Drugs. *Biochemical Pharmacology* 41(4):617-623.
- Kudo, N. 2015. Chapter 6. Metabolism and Pharmacokinetics. In J. C. DeWitt (Ed.), *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*. Switzerland: Humana Press, Springer International Publishing.
- Laws, S, R Cooper, T Stoker 2008. Meeting summary of December 5, 2007 teleconference.
- Liao C, T Wang, L Cui, Q Zhou, S Duan, G Jiang. 2009. Changes in Synaptic Transmission, Calcium Current, and Neurite Growth by Perfluorinated Compounds Are Dependent on the Chain Length and Functional Group. *Environ. Sci Technol* 43:2099-2104.
- Lieder, PH, S Chang, DJ Ehresman, JA Bjork, RR Roy, F Otterdijk, KB Wallace & JL Butenhoff, 2007. Poster Presentation at the annual Society of Toxicology meeting. A 28-day Oral (Gavage) Toxicity Study of Ammonium Perfluorobutyrate (PFBA). *The Toxicologist, Supplement to Toxicological Sciences*. Vol 96(1) March 2007. Abstract 931.
- Mariash, C. 2008. Response to review questions posed by MDH regarding thyroid effects of PFBA.
- Martin, MT, RJ Brennan, W Hu, E Ayanoglu, C Lau, H Ren, CR Wood, JC Corton, RJ Kavlock, DJ Dix. Toxicogenomic Study of Triazole Fungicides and Perfluoroalkyl Acids in Rat Livers Predicts Toxicity and Categorizes Chemicals Based on Mechanism of Toxicity. *Toxicological Sciences* 97(2)595-613, 2007.
- Minnesota Department of Health (MDH). 2008. "Statement of Need and Reasonableness (SONAR), July 11, 2008. Support document relating to Health Risk Limits for Groundwater Rules." from <http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf>.
- Minnesota Department of Health (MDH). 2015. *Minnesota Department of Health. Environmental Health & Biomonitoring Advisory Panel June 9, 2015 Meeting Background Materials*. Retrieved from <http://www.health.state.mn.us/divs/hpcd/tracking/panel/2015Junematerials.pdf>.
- Minnesota Department of Health (MDH). 2017. "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. (May 2011, revised 2017)" from <http://www.health.state.mn.us/divs/eh/risk/guidance/hedrefguide.pdf>.
- NOTOX 2006a. Project 471432 Final Report. Evaluation of the Mutagenic Activity of MTDID 8391 in the Salmonella Typhimurium Reverse Mutation Assay and the Escherichia Coli Reverse Mutation Assay (with Independent Repeat). September 16, 2006.
- NOTOX 2006b. Project 471443 Final Report. Evaluation of the Ability of MTDID 8391 to Induce Chromosomal Aberrations in Cultured Peripheral Human Lymphocytes (with Repeat Experiment). October 24, 2006.

- NOTOX 2007a. Project 470677 Final Report. Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period. June 21, 2007.
- NOTOX 2007b. Project 484492 Final Draft Report. Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period. October, 2007.
- NOTOX 2008a. Morphometric analyses on thyroids from male rats treated with MTDID-8391 under NOTOX Project 470677 (Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period). November 20, 2008.
- NOTOX 2008b. Morphometric analyses on thyroids from 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, BD Buehrer, RL Cox, MC Nunnally, and KH Ramm. 2007a. Protocol EPI-0029. Descriptive Analysis of Perfluorobutyrate (PFBA) and Perfluorobutanesulfonate (PFBS) in Sera Collected in 2006 from Descriptive Analysis of Perfluorobutyrate (PFBA) and Perfluorobutanesulfonate (PFBS) in Sera Collected in 2006 from 3M Cordova Electronic Materials Factory Employees. Final Report. Medical Department, 3M Company. July 30, 2007.
- Olsen GW, ME Ellefson, DC Madsen, BA Gibson and CA Ley. 2007b. Protocol EPI-0030 (amended). Estimation of the Half-life of Serum Elimination of Perfluorobutyrate (PFBA) in Four 3M Male Employees. Final Report. Medical Department, 3M Company. October 22, 2007.
- 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 Process Development Center (CPDC) at the 3M Cottage Grove Facility. Final Report. Medical Department, 3M Company. December 18, 2007.
- Olsen GW, ME Ellefson, WK Reagen, B Gibson and CA Ley. 2007d. Protocol EPI-0026. Descriptive Analysis of Perfluorobutyrate (PFBA) in Sera Collected in 2005 from Former and Current 3M Cottage Grove Employees Who Reside in Selected Communities of Washington and Dakota Counties. Final Report. Medical Department, 3M Company. July 20, 2007.
- Olsen, G., ME Ellefson, DC Mair, TR Church, CL Goldberg, RM Herron, Z Medhdizadehkashi, JB Nobiletti, JA Rios, WK Reagen, LR Zobel. (2011). Analysis of a Homologous Series of Perfluorocarboxylates from American Red Cross Adult Blood Donors, 2000-2011 and 2006. *Environmental Science & Technology*, 45(19), 8022-8029.
- Permadi H, B Lundgren, K Andersson and JW DePierre. 1992. Effects of Perfluoro Fatty Acids on Xenobiotic-metabolizing Enzymes, Enzymes Which Detoxify Reactive Forms of Oxygen and Lipid Peroxidation in Mouse Liver. *Biochemical Pharmacology* 44(6):1183-1191.
- Rodricks, JV. 2007. Letter to Mr. John Stine with attached copy of ENVIRON's drinking water health advisory (DWA).

- Takagi A, K Sai, T Umemura, R Hasegawa and y Kurokawa. 1991. Short-term exposure to the peroxisome proliferators, perfluorooctanoic acid and perfluorodecanoic acid, causes significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats. *Cancer Letters* 57:55-60.
- U.S. Environmental Protection Agency (USEPA). (2011). "Exposure Factors Handbook. Office of Research and Development." from <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252>
- U.S. Environmental Protection Agency (USEPA) - Office of the Science Advisor. (2011a). "Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose." from <http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf>
- 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.
- Wolf CJ, ML Takacs, JE Schmid, C Lau, BD Abbott. 2008. Comparison of the activities of carboxylates and sulfonates of perfluoroalkyl acid (PFAA) of various carbon chain lengths on mouse and human peroxisome proliferator-activated receptor-alpha (PPAR α) in COS-1 cells. Abstract #541. *The Toxicologist CD — An official Journal of the Society of Toxicology*, Volume 102, Number S-1, March 2008
- Zoeller, RT. 2008. Response to review questions posed by MDH regarding thyroid effects of PFBA.