



## Toxicological Summary for: Dichlorofluoromethane

CAS: 75-43-4

Synonyms: DCFM, Freon 21, Refrigerant 21, R-21, HCFC-21, dichloromonofluoromethane, fluorodichloromethane, monofluorofchloromethane

### Health Based Guidance

Only inhalation studies have been conducted with dichlorofluoromethane (DCFM). Insufficient pharmacokinetic data are available for extrapolating from inhalation to oral toxicity. As a result, the toxicity data currently available for DCFM are not sufficient for MDH to develop chemical specific health-based guidance for drinking water.

Evidence suggests that DCFM and chloroform, which are structurally similar, are likely to have similar metabolites and share similar metabolic pathways. Inhalation toxicity data for DCFM and chloroform suggest that chloroform is likely to exhibit similar but slightly greater toxicity than DCFM. MDH has determined that the values derived for chloroform are appropriate to use as Risk Assessment Advice (RAA) for DCFM.

The Minnesota Department of Health (MDH) developed Health Risk Limits (HRLs) for chloroform in 2009. In 2017 MDH re-evaluated chloroform and derived revised health-based values (HBVs).

The RAA values for dichlorodifluoromethane (chloroform 2017 nHBVs) are:

Acute Non-Cancer Risk Assessment Advice (nRAA<sub>Acute</sub>) = Not Derived (Insufficient Data)

Short-term nRAA = 20 µg/L

Additivity endpoint(s): Developmental, Hepatic (liver) system, Immune system

Subchronic nRAA = 20\* µg/L

Additivity endpoint(s): Developmental, Hepatic (liver) system, Immune system

Chronic nRAA = 20\* µg/L

Additivity endpoint(s): Developmental, Hepatic (liver) system, Immune system

Cancer Health Based Value (cHBV) = Not Applicable

\*Set at Short-Term value to be protective of shorter exposures that occur within the subchronic and chronic durations.

For additional information on the 2017 derivation of HBVs for chloroform and additivity endpoints see: [Toxicological Summary for Chloroform](#)

**Volatile:** Yes (moderate)

**Summary of Guidance Value History:**

In 2009, MDH conducted a review of the available toxicity data for DCFM. Oral guidance values were not developed at the time. A toxicological summary was published stating that Risk Assessment Advice (RAA) was considered but could not be derived due to insufficient chemical-specific data. In 2015, MDH re-evaluated DCFM and determined that a surrogate approach could be used to develop health-based guidance. The assessment identified chloroform as an appropriate surrogate for DCFM Risk Assessment Advice. In 2016, the short term, subchronic and chronic RAA values were lowered from 30 µg/L to 20 µg/L due a re-evaluation of the chloroform guidance.

**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?	No	No <sup>1</sup>	Yes	Yes	Yes
Effects observed?	-	-	Yes <sup>2</sup>	Yes <sup>3</sup>	Yes <sup>4</sup>

**Comments on extent of testing or effects:**

General note: There are no oral studies for DCFM available. The water guidance levels for chloroform are expected to be protective against the adverse effects of DCFM. For additional information see: [Chloroform Chemical Summary Sheet](#).

<sup>1</sup> There are no known studies that evaluate the immunotoxicity of DCFM. The short-term and subchronic chloroform guidance values are based on decreased humoral immunity.

<sup>2</sup> In an inhalation study, pregnant rats exposed to DCFM at 10,000 ppm (42,700 mg/m<sup>3</sup>) for 6 hours per day on gestational days 6 to 15 exhibited decreased maternal body weight gain and increased preimplantation loss. For comparison, decreased maternal body weight gain due to chloroform exposure occurred at 10 ppm (49 mg/m<sup>3</sup>) for 7 hours per day on gestational days 7 to 16. Oral developmental studies of chloroform show that doses that are maternally toxic may also be toxic to the fetus and cause the same types of liver damage as observed in adult animals. Developmental effects are identified as short-term co-critical effects for chloroform.

<sup>3</sup> A single oral two-generation study on chloroform has been conducted. Changes in the epididymis were noted at doses over 800 times higher than the short-term and subchronic reference doses; reproductive capacity was not affected. The epididymal effects are subchronic co-critical effects for chloroform.

<sup>4</sup> High inhalation exposures to DCFM lead to CNS depression and narcotic effects. Similar effects were seen for chloroform at very high acute oral doses (> 9000 times higher than the short-term, subchronic, and chronic reference dose). Additional neurotoxic effects of changes in operant behavior occur at chloroform doses >2000 times higher than the subchronic and chronic reference dose.

### Resources Consulted During Review:

ACGIH (1980). Dichlorofluoromethane. Documentation of the Threshold Limit Values. Cincinnati, OH, American Conference of Governmental Industrial Hygienists: 132.

Acros Organics. (2015, 02/10/2015). "SDS for carbon tetrabromide." from <https://www.fishersci.com/shop/msdsproxy?productName=AC108410050&productDescription=CARBON+TETRABROMIDE%252C+99%2525+5GR&catNo=AC108410050&vendorId=VN00032119&storeId=10652>.

Acros Organics. (2015, 2/10/2015). "SDS for iodoform." from <https://www.fishersci.com/shop/msdsproxy?storeId=10652&productName=AC149120050>.

Airgas. (2013, 10/21/2013). "MSDS for dichlorofluoromethane (R-21)." from <http://airgas.com/msds/016851.pdf>.

Airgas. (2015, 5/18/2013). "SDS for difluoromethane (R-32)." from <https://www.airgas.com/msds/001054.pdf>.

AquaPhoenix Scientific. (2015, 5/7/2015). "SDS for bromoform." from [https://www.fishersci.com/content/dam/fishersci/en\\_US/documents/programs/education/regulatory-documents/sds/chemicals/chemicals-b/S25659.pdf](https://www.fishersci.com/content/dam/fishersci/en_US/documents/programs/education/regulatory-documents/sds/chemicals/chemicals-b/S25659.pdf).

Aran'ina, T. (1972). "Effects of aliphatic hydrocarbons and fluorinated and chlorinated derivatives on the content of nucleic acids in animal tissues during embryogenesis." Permsk. Gos. Med. Inst. **110**: 69-71.

Aviado, D. M. (1973). Toxicity of propellants. 4th Annual Conference on Environmental Toxicology. Fairborn, OH, Aerospace Medical Research Laboratory. Report Number AMRL-TR-73-125.

Baeder, C. and T. Hoffman (1991). Initial submission-chloroform: supplementary inhalation embryotoxicity study in Wistar rats (final report) with attachments and cover letter dated 12/24/91. NTIS/OTS0535017. EPA/OTS Doc#8-920000566. Study title: Chloroform: supplementary inhalation embryotoxicity study in Wistar rats. By C. Baeder and T. Hoffmann. September 12, 1991. Performed by Hoechst Aktiengesellschaft, Germany, Sponsored by Hoechst AG and Dow Europe SA. Report No. 91.0902.

Baeder, C. and T. Hofmann (1991). Initial Submission: Chloroform: Supplementary Inhalation Embryotoxicity Study in Wistar Rats (Final Report) with Attachments and Cover Letter Dated 122491. TSCA Submissions. USEPA, Dow Chemical Company.

Baeder, C. and T. Hofmann (1999). Support: Supplementary Inhalation Embryotoxicity Study of Chloroform in Wistar Rats - Study Amendments, with Cover Letter Dated 062593. TSCA Submissions. USEPA, Dow Chemical Company.

Battino, R., P. G. Seybold and F. C. Campanell (2011). "Correlations Involving the Solubility of Gases in Water at 298.15 K and 101325 Pa." Journal of Chemical & Engineering Data **56**(4): 727-732.

Belej, M. A., D. G. Smith and D. M. Aviado (1974). "Toxicity of aerosol propellants in the respiratory and circulatory systems. IV. Cardiotoxicity in the monkey." Toxicology **2**: 381-395.

Bruckner, J. V., W. F. MacKenzie, S. Muralidhara, R. Luthra, G. M. Kyle and D. Acosta (1986). "Oral toxicity of carbon tetrachloride: acute, subacute, and subchronic studies in rats." Fundam Appl Toxicol **6**(1): 16-34.

Brusick, D. J. (1976). Mutagenicity evaluation of Genetron R 21. Kensington, MD, Litton Bionetics, Inc.

Cheshchevik, V. T., I. K. Dremza, E. A. Lapshina, S. V. Zabrodskaia, J. Kujawa and I. B. Zavodnik (2011). "Corrections by melatonin of liver mitochondrial disorders under diabetes and acute intoxication in rats." Cell Biochem Funct **29**(6): 481-488.

Daugherty, J. (1998). Solubility of Common Contaminants. Assessment of Chemical Exposures: Calculation Methods for Environmental Professionals. K. McCombs and A. W. Starkweather Jr. Boca Raton, FL, CRC Press LLC: 402.

DuPont. (2005, 06/27/2005). "MSDS for "FREON" 11." from [http://www.hudsonotech.com/wp-content/themes/hudson/pdfs/msds/R-11/DUPONT\\_R-11\\_6-27-05.pdf](http://www.hudsonotech.com/wp-content/themes/hudson/pdfs/msds/R-11/DUPONT_R-11_6-27-05.pdf).

EMD Chemicals. (2009, 4/2/2009). "MSDS for chloroform (LD50)." from <http://www.unl.edu/cahoonlab/Chloroform%20MSDS.pdf>.

Fabel, M. R., R. Wettengel and W. Hartmann (1972). "Myokardischämie und Arrhythmien durch den Gebrauch von Dosieraerosolen beim Menschen?" Deutsche Medizinische Wochenschrift **97**: 428-431.

Fisher Scientific. (2009, 07/20/2009). "MSDS for carbon tetrachloride." from <http://www.elac.edu/academics/departments/chemistry/chemistrydocuments/docs/C/carbon%20tetrachloride.pdf>.

Gemma, S., L. Vittozzi and E. Testai (2003). "Metabolism of chloroform in the human liver and identification of the competent P450s." Drug Metab Dispos **31**(3): 266-274.

Graham, R. C. (1985). Review of available toxicity literature (published and unpublished). Wilmington, DE, Du Pont Co.

Gross, P. M. and J. H. Saylor (1931). "The Solubilities of Certain Slightly Soluble Organic Compounds in Water." J. Am. Chem. Soc. **53**(5): 1744-1751.

Gutmann, V. and G. Resch (1997). "Hydrophobic interactions in aqueous solutions: Their operation in living systems." J Phys Org Chm **10**(5): 335-342.

Heywood, R., R. J. Sortwell, P. R. Noel, A. E. Street, D. E. Prentice, F. J. Roe, P. F. Wadsworth, A. N. Worden and N. J. Van Abbe (1979). "Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs." J Environ Pathol Toxicol **2**(3): 835-851.

Honeywell. (2004, 01/2004). "MSDS for Genetron 500." from [http://msds-resource.honeywell.com/ehswww/hon/result/result\\_single.jsp?P\\_LANGU=E&P\\_SYS=1&C001=](http://msds-resource.honeywell.com/ehswww/hon/result/result_single.jsp?P_LANGU=E&P_SYS=1&C001=)

[MSDS&C997=C100%3BESDS\\_US%2BC102%3BUS%2B1000&C100=\\*&C101=\\*&C102=\\*&C005=000000011260&C008=&C006=HON&C013=+](#)

JACC (1990). Dichlorofluoromethane (HCFC-21). J. A. o. C. Chemicals. Brussels, Belgium, ECETOC: 26.

Kelly, D. P., R. Culic, H. J. Trochimowicz and W. F. Fayerweather (1978). Inhalation teratology studies on three fluorocarbons. 17th Annual Meeting of the Society of Toxicology. San Francisco, CA, Toxicology and Applied Pharmacology. **45**: 293.

Lab Chem. (2009, 9/3/2009). "MSDS for chloroform (LC50)." from <http://www.labchem.com/tools/msds/msds/LC13040.pdf>

Larson, J. L., M. V. Templin, D. C. Wolf, K. C. Jamison, J. R. Leininger, S. Mery, K. T. Morgan, B. A. Wong, R. B. Conolly and B. E. Butterworth (1996). "A 90-day chloroform inhalation study in female and male B6C3F1 mice: implications for cancer risk assessment." Fundam Appl Toxicol **30**(1): 118-137.

Lindberg, D. C. (1979). Subacute Inhalation Toxicity Study with Genetron 21 in Albino Rats. Decatur, IL, Industrial Bio-Test Laboratories.

Luke, B. T., G. H. Loew and A. D. McLean (1988). "Theoretical Investigation of the Anaerobic Reduction of Halogenated Alkanes by Cytochrome P-450. 2. Vertical Electron Affinities of Chlorofluoromethanes as a Measure of Their Activity." J Am Chem Soc **110**(11): 3396-3400.

Matheson Tri-Gas. (1999, 3/16/1999). "MSDS for dibromomethane." from <http://www.megs.ca/MSDS/Pdf/Dibromomethane.PDF>.

Matheson Tri-Gas. (2008, 12/11/2008). "MSDS for Methyl bromide." from <https://www.mathesongas.com/pdfs/msds/MAT14300.pdf>.

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>.

MDH. (2015). "Human Health-Based Water Guidance Table - EH: Minnesota Department of Health." from <http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html>.

Merck. (2013, 06/25/2013). "SDS for diiodomethane." from [http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=8&ved=0CE4QFjAH&url=http%3A%2F%2Fwww.merckmillipore.com%2Fproducts%2F818153%3Fattachments%3DMSDSdetail%26doccountry%3DUSA%26doclanguage%3DEN&ei=F0p1Vb\\_WHo73oAT6-IPYDg&usq=AFQjCNH3RJ4PNS98fB0TzYKJzOU\\_EYPslw&sig2=-qKQTRpM9LjnEODCdfFNjA&cad=rja](http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=8&ved=0CE4QFjAH&url=http%3A%2F%2Fwww.merckmillipore.com%2Fproducts%2F818153%3Fattachments%3DMSDSdetail%26doccountry%3DUSA%26doclanguage%3DEN&ei=F0p1Vb_WHo73oAT6-IPYDg&usq=AFQjCNH3RJ4PNS98fB0TzYKJzOU_EYPslw&sig2=-qKQTRpM9LjnEODCdfFNjA&cad=rja).

Minnesota Department of Health (MDH). (2011). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses." from <http://www.health.state.mn.us/divs/eh/risk/guidance/hedrefguide.pdf>.

Mullett, T., T. Zoeller, H. Bingham, C. J. Pepine, X. E. Prida, R. Castenholz and R. Kirby (1987). "Fatal hydrofluoric acid cutaneous exposure with refractory ventricular fibrillation." J Burn Care Rehabil **8**(3): 216-219.

Munson, A. E., L. E. Sain, V. M. Sanders, B. M. Kauffmann, K. L. White, Jr., D. G. Page, D. W. Barnes and J. F. Borzelleca (1982). "Toxicology of organic drinking water contaminants: trichloromethane, bromodichloromethane, dibromochloromethane and tribromomethane." Environ Health Perspect **46**: 117-126.

Nagano, K., T. Sasaki, Y. Umeda, T. Nishizawa, N. Ikawa, H. Ohbayashi, H. Arito, S. Yamamoto and S. Fukushima (2007). "Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice." Inhal Toxicol **19**(13): 1089-1103.

Narotsky, M. G., C. F. Brownie and R. J. Kavlock (1997). "Critical period of carbon tetrachloride-induced pregnancy loss in Fischer-344 rats, with insights into the detection of resorption sites by ammonium sulfide staining." Teratology **56**(4): 252-261.

Narotsky, M. G., R. A. Pegram and R. J. Kavlock (1997). "Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats." Fundam Appl Toxicol **40**(1): 30-36.

NRC (1984). Emergency and Continuous Exposure Limits for Selected Airborne Contaminants. B. o. T. a. E. H. H. Committee on Toxicology, Commission on Life Sciences. Washington, D.C., National Academy Press. **2**: 41-45.

Nuckolls, A. H. (1935). Report on the comparative life, fire, and explosion hazards of dichloromonofluoromethane (FC-21). Chicago, IL: 15.

OSHA. (2015). "Chemical Sampling Information | Dichloromonofluoromethane." from [https://www.osha.gov/dts/chemicalsampling/data/CH\\_233800.html](https://www.osha.gov/dts/chemicalsampling/data/CH_233800.html).

Peter, H., J. G. Filser, L. von Szentpaly and H. J. Wiegand (1986). "Different pharmacokinetics of dichlorofluoromethane (CFC 21) and chlorodifluoromethane (CFC 22)." Arch Toxicol **58**(4): 282-283.

Praxair. (2014, 10/01/2014). "SDS for chlorodifluoromethane (R-22)." from <http://www.praxair.com/-/media/praxairus/documents/sds/halocarbon-22-chcif2-safety-data-sheet-sds-p4667.pdf?la=en&hash=7894DFEA60A891CDFE4C5A58211C76C012EFF98B>

Praxair. (2015, 3/6/2015). "SDS for methyl chloride (R-40)." from <http://www.praxair.com/-/media/documents/sds/methyl-chloride-ch3cl-safety-data-sheet-sds-p4622.pdf?la=en>

Rottenberg, H. (1983). "Uncoupling of oxidative phosphorylation in rat liver mitochondria by general anesthetics." Proc Natl Acad Sci USA **80**: 3313-3317.

Ryan, T. A., C. Ryan, E. A. Seddon and K. R. Seddon (1996). Asymmetric carbonyl halides. Topics in Inorganic and General Chemistry: Phosgene and Related Carbonyl Halides. Amsterdam, Netherlands, Elsevier. **24**: 685-741.

Sander, R. (1999). Compilation of Henry's Law Constants for Inorganic and Organic Species of Potential Importance in Environmental Chemistry. Mainz, Germany, Max-Planck Institute of Chemistry.

Sciencelab.com. (2013, 5/21/2013). "MSDS for methyl iodide." from <http://www.sciencelab.com/msds.php?msdsId=9927669>.

Sherman, H. (1974). "Long-term feeding studies in rats and dogs with dichlorodifluoromethane (Freon 12 Food Freezant). Haskell Laboratory for Toxicology and Industrial Medicine Report No. 24-74."

Smialowicz, R. J., J. E. Simmons, R. W. Luebke and J. W. Allis (1991). "Immunotoxicologic assessment of subacute exposure of rats to carbon tetrachloride with comparison to hepatotoxicity and nephrotoxicity." Fundam Appl Toxicol **17**(1): 186-196.

Tappan, C. H. and R. S. Waritz (1964). Report No. 128-064. Wilmington, DE, Du Pont Co.

Templin, M. V., A. A. Constan, D. C. Wolf, B. A. Wong and B. E. Butterworth (1998). "Patterns of chloroform-induced regenerative cell proliferation in BDF1 mice correlate with organ specificity and dose-response of tumor formation." Carcinogenesis **19**(1): 187-193.

Templin, M. V., J. L. Larson, B. E. Butterworth, K. C. Jamison, J. R. Leininger, S. Mery, K. T. Morgan, B. A. Wong and D. C. Wolf (1996). "A 90-day chloroform inhalation study in F-344 rats: profile of toxicity and relevance to cancer studies." Fundam Appl Toxicol **32**(1): 109-125.

Trochimowicz, H. J., J. P. Lyon, D. P. Kelly and T. Chiu (1977). Ninety-day inhalation toxicity studies on two fluorocarbons. 16th Annual Meeting of the Society of Toxicology. Toronto, Canada, Toxicology and Applied Pharmacology. **41**: 200.

Trochimowicz, H. J., B. L. Moore and T. Chiu (1977). Subacute Inhalation Toxicity Studies on Eight Fluorocarbons. 16th Annual Meeting of the Society of Toxicology. Toronto, Canada, Toxicology and Applied Pharmacology. **41**: 198-199.

US Pharmacopeia. (2012, 12/28/2012). "SDS for methylene chloride." from <http://www.usp.org/pdf/EN/referenceStandards/msds/1601441.pdf>.

USAPHC (2013). Environmental Health Risk Assessment and Chemical Exposure Guidelines for Deployed Military Personnel. U. S. A. P. H. Command. Aberdeen Proving Ground, Maryland, Department of Defense: 536.

USEPA. (1988). "Recommendations for and Documentation of Biological Values for Use in Risk Assessment." from <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855>.

USEPA. (1995). "Dichlorodifluoromethane (CASRN 75-71-8) | IRIS | US EPA." from <http://www.epa.gov/iris/subst/0040.htm>.

USEPA (2001). Toxicological Review of Chloroform (CAS No. 67-66-3): In Support of Summary Information on the Integrated Risk Information System (IRIS). U. S. E. P. Agency. Washington, D.C., U.S. Environmental Protection Agency: 112.

USEPA (2002). A Review of the Reference Dose and Reference Concentration Processes. U. S. E. P. A. Risk Assessment Forum. Washington, D.C., U.S. Environmental Protection Agency: 192.

USEPA. (2010). "Carbon tetrachloride (CASRN 56-23-5) | IRIS | US EPA." from <http://www.epa.gov/iris/subst/0020.htm>.

USEPA. (2011). "Recommended Use of Body Weight<sup>3/4</sup> as the Default Method in Derivation of the Oral Reference Dose." from <http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf>.

USEPA. (2015, 10/01/1992). "Bromomethane (CASRN 74-83-9) | IRIS | US EPA." from <http://www.epa.gov/iris/subst/0015.htm>.

USEPA. (2015). "Drinking Water Contaminants | US EPA." from <http://water.epa.gov/drink/contaminants/index.cfm#organic>.

USEPA. (2015, 08/01/1992). "Trichlorofluoromethane (CASRN 75-69-4) | IRIS | US EPA." from <http://www.epa.gov/iris/subst/0120.htm>.

Van Auken, O. W. and R. H. Wilson (1973). "Halogenated Hydrocarbon Induced Reduction in Coupling Parameters of Rabbit Liver and Mung Bean Mitochondria." Naturwissenschaften **60**: 259.

Veech, R. L., L. V. Eggleston and H. A. Krebs (1969). "The redox state of free nicotinamide-adenine dinucleotide phosphate in the cytoplasm of rat liver." Biochem J **115**(4): 609-619.

Waller, C. L. and J. D. McKinney (1993). "Theoretical Investigation into the Potential of Halogenated Methanes to Undergo Reductive Metabolism." J Comp Chem **14**(12): 1575-1597.

Weigand, W. (1971). "Untersuchungen über die Inhalationstoxizität von Fluorderivaten des Methan, Äthan und Cyclobutan." Zentralblatt für Arbeitsmedizin und Arbeitsschutz **21**: 149-156.