CHLORODIFLUOROMETHANE

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987a).

1. Exposure Data

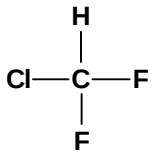
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 75-45-6

Systematic name: Chlorodifluoromethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



$CHClF_2$ Relative molecular mass: 86.47

1.1.3 *Physical properties* (for details, see IARC, 1986)

(*a*) *Boiling-point*: –40.8°C

(*b*) *Melting-point*: –146°C

(*c*) *Conversion factor*: $mg/m^3 = 3.54 \times ppm$

1.2 Production, use and human exposure

Chlorodifluoromethane is produced extensively for use in refrigeration and air conditioning; significant quantities are subsequently released into the atmosphere, resulting in widespread, low-level human exposure. Occupational exposure to chlorodifluoromethane occurs during its production and use (IARC, 1986).

2. Studies of Cancer in Humans

A small study of workers exposed to a mixture of chlorofluorocarbons, including chlorodifluoromethane, was uninformative with regard to the carcinogenic hazard of this chemical due to small numbers of individuals studied (IARC, 1986, 1987a).

3. Studies of Cancer in Experimental Animals

Chlorodifluoromethane was tested for carcinogenicity in one experiment in rats by oral administration and in experiments in rats and mice by inhalation exposure. No increase in tumour incidence was observed in rats after oral administration. The inhalation study in mice was inconclusive for males, and negative results were obtained for females. In the inhalation study in rats, males receiving the high dose had increased incidences of fibrosarcomas and Zymbal gland tumours; negative results were obtained for female rats (IARC, 1986).

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 60 male and 60 female Swiss mice, nine weeks of age, were exposed by inhalation to 0, 1000 or 5000 ppm [0, 3540 or 17 700 mg/m^3] chlorodifluoromethane (FC 22; purity, 99.98%) for 4 h per day on five days per week for 78 weeks. The animals were kept under observation until spontaneous death [survival unspecified]. Full necropsy was performed on all animals. No effects were found on survival or body weight. No difference related to treatment was found in the incidence of benign or malignant tumours (Maltoni *et al*., 1988).

3.1.2 *Rat*

Groups of 60 male and 60 female Sprague-Dawley rats, eight weeks of age, were exposed by inhalation to 0, 1000 or 5000 ppm [0, 3540 or 17 700 mg/m^3] chlorodifluoromethane (FC 22; purity, 99.98%) for 4 h per day on five days per week for 104 weeks. Full necropsy was performed on all animals. No effects were found on survival or body weight. No difference related to treatment was found in the incidence of benign or malignant tumours (Maltoni *et al*., 1988).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Two groups of three male volunteers were exposed by inhalation to chlorodifluoromethane at either 327 or 1833 mg/m^3 for 4 h. The average maximal blood concentrations were 0.25 and 1.36 μg/mL, respectively, and were achieved within 1 h of the beginning of exposure. The average blood/air partition coefficients for chlorodifluoromethane towards the end of the exposure period were 0.82 and 0.76, respectively, and the fat/air partition coefficients were 7.7 and 8.1. Thus, the fat/blood partition coefficient was estimated to be

approximately 10. Three phases for the elimination of chlorodifluoromethane in breath were identified, with estimated half-lives of 0.005, 0.2 and 2.6 h. An average of 2.1% of the inhaled chlorodifluoromethane was recovered from the exhaled air over 26 h and minimal amounts were found in urine. Minimal changes in the fluoride concentration in urine were observed, which is consistent with a low degree of metabolism (Woollen *et al*., 1992).

Two simultaneous accidental, lethal exposures to chlorodifluoromethane alone were associated with concentrations (in μL/mL) of the chemical in body fluid samples taken 16 h after death of: blood, 37.1 and 26.0; urine, 1.7 and 0.9; vitreous humor, 1.0 and 0.7 (Kintz *et al*., 1996).

4.1.2 *Experimental systems*

The metabolism of chlorodifluoromethane has been briefly reviewed (Anders, 1991).

Chlorodifluoromethane is very rapidly cleared from the blood of rats and rabbits exposed by inhalation. Little distribution to tissues or metabolism occurs in rats, with recoveries from expired air as CO_2 in 15–24 h and in the urine, being about 0.1% and 0.02% of the dose, respectively (IARC, 1986).

Chlorodifluoromethane inhaled by male Wistar rats at a concentration of 160 ppm [566 mg/m^3] underwent no detectable metabolism and prior treatment of the rats with either DDT or phenobarbital did not stimulate its metabolic transformation (Peter *et al*., 1986).

4.2 Toxic effects

4.2.1 *Humans*

Although chlorodifluoromethane has low toxicity, it is capable of producing rapid death in people abusing it for euphoric effects (Fitzgerald *et al*., 1993) or in situations of accidental high exposure in occupational circumstances (Kintz *et al*., 1996). Cardiac arrhythmias have been studied in refrigerator repair men who were exposed to chlorodifluoromethane during their work and a comparison group of plumbers. Peak concentrations of chlorodifluoromethane measured during the repair work were 1300–10 000 cm^3/m^3 for times of 2–35 min. No clear connection between exposure and cardiac arrhythmia was found, although one subject had several ventricular ectopic beats that may have been connected with exposure (Antti-Poika *et al*., 1990). There appear to have been no reports of Freons including chlorodifluoromethane causing secondary arterial hypertension prior to two case reports where one of the subjects received an acute, massive, accidental exposure to a mixture of chlorodifluoromethane and dichlorodifluoromethane (Voge, 1996).

4.2.2 *Experimental systems*

Chlorodifluoromethane has low acute toxicity; concentrations of 20% were not lethal to rodents, rabbits or dogs. Exposure to high concentrations causes central nervous

system and myocardial depression. No effect was observed on mortality, haematology or biochemistry in mice or rats exposed to 1000–50 000 ppm [3540–177 000 mg/m^3] for 5 h per day on five days per week for up to 94 weeks (mice) or 131 weeks (rats) (IARC, 1986).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Chlorodifluoromethane causes malformations of the eyes of fetal rats, but has no reproductive effect in male rats and does not cause prenatal toxicity in rabbits following exposure by inhalation (IARC, 1986).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Chlorodifluoromethane is mutagenic to *Salmonella typhimurium* but it did not induce either mutation or gene conversion in *Saccharomyces cerevisiae*. Chlorodifluoromethane did not induce mutations at the *hprt* locus or unscheduled DNA synthesis in mammalian cell lines in the presence or absence of an exogenous metabolic activation system. *In vivo*, it did not induce chromosomal aberrations in bone-marrow cells or dominant lethal effects (IARC, 1987b). These conclusions are supported by a more recent review (WHO, 1991).

5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of chlorodifluoromethane.

There is *limited evidence* in experimental animals for the carcinogenicity of chlorodifluoromethane.

Overall evaluation

Chlorodifluoromethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

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