# Chlorodifluoromethane; CASRN 75-45-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Chlorodifluoromethane

**File First On-Line 11/01/1993**

| Category (section) | Assessment Available? | Last Revised |
|---|---|---|
| **Oral RfD (I.A.)** | not evaluated | |
| **Inhalation RfC (I.B.)** | yes | 11/01/1993 |
| **Carcinogenicity Assessment (II.)** | not evaluated | |

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Chlorodifluoromethane
CASRN — 75-45-6
Primary Synonym — HCFC-22

Not available at this time.

## I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Chlorodifluoromethane
CASRN — 75-45-6
Primary Synonym — HCFC-22
Last Revised — 11/01/1993

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### I.B.1. Inhalation RfC Summary

| Critical Effect | Exposures* | UF | MF | RfC |
|---|---|---|---|---|
| **Increased kidney, adrenal and pituitary weights**<br><br>**Chronic Rat Inhalation Study**<br><br>**Tinston et al., 1981a** | NOAEL: 35,370 mg/cu.m (10,000 ppm)<br>NOAEL(ADJ): 5260 mg/cu.m<br>NOAEL(HEC): 5260 mg/cu.m<br><br>LOAEL: 176,800 mg/cu.m (50,000 ppm)<br>LOAEL(ADJ): 26,300 mg/cu.m<br>LOAEL(HEC): 26,300 mg/cu.m | 100 | 1 | 5E+1 mg/cu.m |

| Critical Effect | Exposures* | UF | MF | RfC |
|---|---|---|---|---|
| **Reduced maternal weight gain**<br>**Rat Developmental Study**<br>**Palmer et al., 1978a** | NOAEL: 3537 mg/cu.m<br>NOAEL(ADJ): 909 mg/cu.m<br>NOAEL(HEC): 909 mg/cu.m<br><br>LOAEL: 176,800 mg/cu.m (50,000 ppm)<br>LOAEL(ADJ): 44,200 mg/cu.m<br>LOAEL(HEC): 44,200 mg/cu.m | | | |

* Conversion Factors and Assumptions -- Tinston et al., 1981a: MW = 86.47. Assuming 25 C and 760 mm Hg, NOAEL(mg/cu.m) = 10,000 ppm x 86.47/24.45 = 35,400 mg/cu.m. NOAEL(ADJ) = NOAEL(mg/cu.m) x 5 hours/24 hours x 5 days/7 days = 5260 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. Since the b:a lambda values are unknown for the experimental animals species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = 5260 x [b:a lambda(a)/b:a lambda(h)] = 5260 mg/cu.m.

Palmer et al., 1978a: MW = 86.47. Assuming 25 C and 760 mm Hg, LOAEL(mg/cu.m) = 50,000 ppm x 86.47/24.45 = 176,800. LOAEL(ADJ) = LOAEL(mg/cu.m) x 6 hours/24 hours x 7 days/7 days = 44,200 mg/cu.m. The LOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. Since the b:a lambda values are unknown for the experimental animals species (a) and humans (h), a default value of 1.0 is used for this ratio. LOAEL(HEC) = 44,200 x [b:a lambda(a)/b:a lambda(h)] = 44,200 mg/cu.m.

**I.B.2. Principal and Supporting Studies (Inhalation RfC)**

Tinston, D.J., I.S. Chart, M.J. Godley, C.W. Gore, M.H. Litchfield, and M. Robinson. 1981a. Chlorodifluoromethane (CFC 22): Long term inhalation study in the rat. Report No. CTL/P/548. Imperial Chemical Industries Limited, Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Palmer, A.K., D.D. Cozens, R. Clark, and G.C. Clark. 1978a. Effect of Arcton 22 on pregnant rats: Relationship to anophthalmia and microphthalmia. Report No. ICI 174/78208. Huntingdon Research Centre, Huntingdon, UK.

Tinston et al. (1981a) exposed groups of 80 Alderley Park Wistar-derived rats/sex to 0 (two control groups), 1000, 10,000, or 50,000 ppm (0, 3540, 35,370, and 176,800 mg/cu.m, respectively) HCFC-22 for 5 hours/day, 5 days/week (duration-adjusted concentrations = 0, 526, 5260, 26,300 mg/cu.m, respectively) for up to 118 weeks (females) or 131 weeks (males). Ten animals/group were sacrificed at 52 weeks for hematological, clinical chemistry, and histopathological evaluation. Remaining animals were sacrificed when there was 80% mortality in all groups. The animals were exposed in 2-cu.m stainless steel chambers with an air flow of 280 L/minute. The test atmosphere was generated by dilution of HCFC-22 with air and was measured periodically by gas chromatography. Concentrations were found to be within 15% of target. Hematological and clinical chemistry parameters were measured, and urinalysis was conducted prior to sacrifice. Histopathological examination of approximately 30 tissues (including the lungs and nasal cavity) was conducted on all animals that died during the study or were sacrificed. No exposure-related effects on survival, clinical signs, body weight, hematology, clinical chemistry, or urinalysis parameters were observed. The female rats in the 50,000-ppm group exhibited a statistically significant increase in liver (absolute and relative), kidney (absolute), adrenal (absolute), and pituitary (absolute, at interim sacrifice--pituitaries were not weighed at terminal sacrifice) weights. No nonneoplastic histopathological changes attributable to exposure to HCFC-22 were observed. The liver weight effect was not considered adverse because it did not exceed a 10% weight change and there was no histopathology observed. Based on effects on kidney, adrenal, and pituitary weight, a NOAEL of 10,000 ppm [NOAEL(HEC) = 5260 mg/cu.m] and a LOAEL of 50,000 ppm [LOAEL(HEC) = 26,300 mg/cu.m] can be estimated.

Palmer et al. (1978a) conducted a large developmental study in an attempt to elucidate the role of CFC-22 exposure in the eye lesion seen in the previous studies (see Culik et al., 1977, and Culik and Crowe, 1978, in the Additional Studies/Comments section). In this study, an experimental design was used in which 34 control pregnant rats were used, and 22/group were exposed to 100, 1000, or 50,000 ppm of CFC-22 (354, 3,540, or 176,800 mg/cu.m, respectively) for 6 hours/day on gestation days 6-15. This protocol was repeated 19 times so that more than 6000 control fetuses and 4000 fetuses from each exposed group were thoroughly examined for the eye defect. Maternal body weight gain was consistently lower in the dams exposed to 50,000 ppm. The average maternal weight on day 20 was lower than controls in 15/19 replicate experiments, and the overall average maternal weight in the treated groups was 96.6% of the controls. The average weight gain from day 6-17 of gestation was decreased by 3, 3, and 15% in the groups exposed to 100, 1000, and 50,000 ppm, respectively. Although this effect was statistically significant in all exposed groups, it is considered to be adverse only in the group exposed to 50,000 ppm. No other adverse effects were noted in the dams, and there was no evidence of exposure-related effects on pregnancy outcome or the incidence of gross terata. In the animals exposed to 50,000 ppm, fetal weight was lower than in controls, and the difference was statistically significant in three of the individual repetitions as well as for all repetitions using a nonparametric rank sum

analysis. The eye abnormalities (small or missing eye) were noted again in all exposure groups, but statistical significance for these effects was achieved only in the 50,000-ppm group. The combined incidences of microphthalmia and anophthalmia were 3/607, 5/393, 3/390, and 10/383 in the control, 100, 1000, and 50,000-ppm groups, respectively. Additional data on the control incidence of the eye effects during 10 years after the Palmer et al. (1978a) study was conducted are presented in European Chemical Industry Ecology and Toxicology Center (ECETOC) (1989). The data were analyzed in blocks of 19 studies, and the control incidence in the first six blocks was similar to the controls in the Palmer study, while in later studies, the control incidence increased (0.4-2.4% in the last four blocks) and, in one experiment, was similar to the incidence found in the high-dose group in the Palmer study (2.6%). The incidence of the eye abnormality in the high-concentration group in the Palmer et al. (1978a) study is significantly increased compared with the overall controls in the studies conducted in the 10-year period after the study (ECETOC, 1989), adding strength to the interpretation that this is an adverse, treatment-related effect. This study identifies a LOAEL for maternal weight, fetal weight, and fetal abnormalities at 50,000 ppm. The LOAEL(HEC) is 176,800 mg/cu.m for the fetal effects (no duration adjustment is applied) and 44,200 mg/cu.m for the maternal toxicity (exposure is adjusted for duration).

### I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — The uncertainty factor of 100 reflects a factor of 10 to protect unusually sensitive individuals, 3 for interspecies extrapolation, and 3 for database deficiencies including lack of a two-generation reproductive study.

MF — None

### I.B.4. Additional Studies/Comments (Inhalation RfC)

A long-term study was conducted in Alderley Park Swiss-derived mice (Tinston et al., 1981b). In this study, 80 mice/sex/group were exposed to 0, 1000, 10,000, or 50,000 ppm (0, 3540, 35,370, and 176,800 mg/cu.m, respectively) HCFC-22 for 5 hours/day, 5 days/week (duration-adjusted concentrations = 0, 526, 5260, and 26,300 mg/cu.m, respectively) for up to 83 weeks (males) or 94 weeks (females). Ten animals/group were sacrificed at 38 weeks for hematological, clinical chemistry, and histopathological evaluation. The same clinical, gross, and microscopic evaluations were conducted on the mice as those described for the rats in the chronic rat study (Tinston et al., 1981a). No exposure-related effects on body weight gain; hematological, clinical chemistry, or urinalysis parameters; or gross or microscopic pathology were noted. Data on organ weights were not reported. Hyperactivity in the 50,000-ppm males was the only consistent effect noted that could be attributed to HCFC-22 exposure. However, no definition of hyperactivity or scoring criteria was provided. Nonneoplastic lesions seen in the respiratory tract

at comparable incidences in both the exposed and control groups were indicative of Sendai virus infection. This study identifies a LOAEL for the clinical observation of hyperactivity of 50,000 ppm [LOAEL(HEC) = 26,300 mg/cu.m] and a NOAEL of 10,000 ppm [NOAEL(HEC) = 5260 mg/cu.m].

Two subchronic inhalation toxicity studies support the relatively low toxicity of HCFC-22 seen in the chronic studies. Leuschner et al. (1983) exposed 20 Sprague-Dawley rats/sex/group and 3 beagle dogs/sex/group to 0, 5000 (17,680 mg/cu.m, dogs), or 10,000 ppm (35,370 mg/cu.m, rats) HCFC-22 for 6 hours/day, 7 days/week, for 13 weeks by whole-body exposure [duration-adjusted concentrations = 0, 4420 (dogs), or 8840 (rats) mg/cu.m]. Clinical signs, body weight, hematology, clinical chemistry, urinalysis, organ weights, and histopathology were assessed in both rats and dogs, and electrocardiogram and circulatory function (blood pressure with and without norepinephrine stress) were also evaluated in the dogs. Microscopic examination of 27 organs (not specified) was carried out on both rats and dogs at study termination. No exposure-related effects on any of the parameters evaluated were noted in either species. This study identifies a free-standing NOAEL of 5000 ppm [NOAEL(HEC) = 4420 mg/cu.m] in dogs and 10,000 ppm in rats [NOAEL(HEC) = 8840 mg/cu.m].

Lee and Suzuki (1981) exposed groups of 16 male Sprague-Dawley rats to 0 or 50,000 ppm HCFC-22 for 5 hours/day, 7 days/week for 8 weeks (duration- adjusted concentrations = 0 or 36,800 mg/cu.m, respectively). Six rats/group were sacrificed at 8 weeks, and the rest were used in a fertility study (discussed below). The only exposure-related effects noted were a slight decrease in prostate weight (without accompanying histopathological changes), an increase in plasma cholesterol, and decreases in plasma glucose and triglycerides. The toxicological significance of these changes is not clear because functional studies on adrenal or hepatic function were not undertaken, and there were no histopathological changes in these organs. Nevertheless, a LOEL of 50,000 ppm [LOEL(HEC) = 36,800 mg/cu.m] can be estimated from this study.

One study is available that investigated the potential reproductive toxicity of HCFC-22 in male animals. As discussed previously, Lee and Suzuki (1981) exposed male Sprague-Dawley rats to 0 or 50,000 ppm HCFC-22 (duration- adjusted concentrations = 0 or 36,800 mg/cu.m, respectively) 5 hours/day, 7 days/week for 8 weeks. Six rats/group were sacrificed at this time and the rest were used in the fertility study. In the animals sacrificed immediately after the last exposure, prostatic fructose and acid phosphatase activity were measured, as well as plasma follicle stimulating hormone and luteinizing hormone. The surviving animals were then serially mated with virgin unexposed females for 7-day periods for a total 10 weeks. The mated females were killed 9 days after removal from the males and the number of corpora lutea, total implants, live implants, resorption sites, and dead implants were counted. Except for the decrease in

prostate weight mentioned above, no exposure- related effects were noted in any of these parameters.

Two developmental studies in rats were reported by Culik et al. (1977). In the first study, 21 or 22 female albino rats were exposed to 0, 1000, or 10,000 ppm CFC-22 for 6 hours/day. Half of the rats were exposed on days 4-13 of gestation and half on days 6-15 of gestation. No maternal toxicity (i.e., changes in body weight gain, clinical signs, or gross pathology) was observed in this study. Indices of pregnancy outcome and fetotoxicity were also unaffected by exposure to HCFC-22. However, rare eye abnormalities (small or missing eyes) were noted in one fetus from the lower concentration and in two fetuses from the higher concentration groups. Because this abnormality has a low spontaneous incidence, a second study was performed with a larger number of animals. Groups of 33-35 pregnant rats were exposed to 0, 500, 1000, or 20,000 ppm CFC-22 for 6 hours/day on days 6-15 of gestation. As in the first study, there were no effects on maternal or fetal toxicity and no malformations except the eye defect. One litter from each exposed group showed microphthalmia (small eye) or anophthalmia (absent eye), and in the 1000-ppm litter, two pups were affected. Although not statistically significant, these findings are suggestive of a developmental effect because of the relative rarity of this lesion. The incidence was reported to be statistically significant compared to historical control data, which were cited as one fetus with microphthalmia in 411 litters. This finding was not considered to be adverse.

A follow-up to the Culik et al. (1977) studies was reported by Culik and Crowe (1978), in which the same rat strain (35-41/group) was exposed on days 6-15 of gestation to 0, 100, 300, or 10,000 ppm CFC-22. There were no effects on maternal weight, clinical signs, gross pathology, or in indices of pregnancy outcome. No effects on fetal weight or crown-rump length were observed. The only malformation observed was unilateral microphthalmia in three fetuses, one in the group exposed to 100 ppm and two (from different litters) exposed to 10,000 ppm.

No adverse maternal or developmental effects were noted in rabbits exposed to concentrations of HCFC-22 up to 50,000 ppm (176,800 mg/cu.m) (Palmer et al. 1978b).

Pharmacokinetic data indicate that HCFC-22 is rapidly absorbed and eliminated following inhalation exposure (Litchfield and Longstaff, 1984; Sakata et al., 1981). Peter et al. (1986) demonstrated in studies in rats that HCFC-22 undergoes very little metabolism in the body and is eliminated largely unchanged.

### I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

The principal studies were well-conducted, used a sufficient number of animals, and identified a NOAEL and a LOAEL. The chronic studies are supported by subchronic studies, and the developmental toxicity following inhalation exposure has been adequately studied. The database is given a medium-to-high level of confidence because the chronic inhalation study in mice lacks reporting of some endpoints and because the database lacks a two- generation reproductive study. Medium to high confidence in the RfC follows.

### I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 09/23/1992

Verification Date — 09/23/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Chlorodifluoromethane conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

### I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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## II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Chlorodifluoromethane
CASRN — 75-45-6
Primary Synonym — HCFC-22

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

## III. [reserved]
## IV. [reserved]
## V. [reserved]

## VI. Bibliography

Substance Name — Chlorodifluoromethane
CASRN — 75-45-6
Primary Synonym — HCFC-22

### VI.A. Oral RfD References

None

### VI.B. Inhalation RfC References

Culik, R., D.P. Kelly, and B.A. Burgess. 1977. Embryotoxic and teratogenic studies in rats with inhaled chlorodifluoromethane (FC-22). Haskell Laboratory Report No. 970-76.

Culik, R. and C.D. Crowe. 1978. Embryotoxic and teratogenic studies in rats with inhaled chlorodifluoromethane (FC-22), third study. Haskell Laboratory Report No. 314-78.

ECETOC (European Chemical Industry Ecology and Toxicology Center). 1989. Joint Assessment of Commodity Chemicals. No. 9. Chlorodifluoromethane. European Chemical Industry Ecology and Toxicology Center. Brussels, Belgium.

Lee, I.P. and K. Suzuki. 1981. Studies on the male reproductive toxicity of Freon 22. Fund. Appl. Toxicol. 1: 266-270.

Leuschner, F., B. W. Neumann, and F. Hubscher. 1983. Report on subacute toxicological studies with several fluorocarbons in rats and dogs by inhalation. Arzneim.-Forsch. 33(10): 1475-1476.

Litchfield, M.H. and E. Longstaff. 1984. Summaries of toxicological data. The toxicological evaluation of chlorofluorocarbons 22 (CFC 22). Fd. Chem. Toxicol. 22(6): 465-475.

Palmer, A.K., D.D. Cozens, R. Clark, and G.C. Clark. 1978a. Effect of Arcton 22 on pregnant rats: Relationship to anophthalmia and microphthalmia. Report No. ICI 174/78208. Huntingdon Research Centre, Huntingdon, UK.

Palmer, A.K., D.D. Cozens, R. Clark, and G.C. Clark. 1978b. Effect of Arcton 22 on pregnancy of the New Zealand white rabbit. Report No. ICI 177/78505. Huntingdon Research Centre, Huntingdon, UK.

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

Sakata, M., H. Kazama, A. Miki, A. Yoshida, M. Haga, and M. Morita. 1981. Acute toxicity of fluorocarbon-22: Toxic symptoms, lethal concentration, and its fate in rabbit and mouse. Toxicol. Appl. Pharmacol. 59: 64-70.

Tinston, D.J., I.S. Chart, M.J. Godley, C.W. Gore, M.H. Litchfield, and M. Robinson. 1981a. Chlorodifluoromethane (CFC 22): Long term inhalation study in the rat. Report No. CTL/P/548. Imperial Chemical Industries Limited, Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Tinston, D.J., I.S. Chart, M.J. Godley, C.W. Gore, B.A. Gaskell, and M.H. Litchfield. 1981b. Chlorodifluoromethane (CFC 22): Long term inhalation study in the mouse. Report No. CTL/P/547. Imperial Chemical Industries Limited, Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

## VI.C. Carcinogenicity Assessment References

None

## VII. Revision History

Substance Name — Chlorodifluoromethane
CASRN — 75-45-6
Primary Synonym — HCFC-22

| Date | Section | Description |
|---|---|---|
| **11/01/1993** | I.B. | Inhalation RfC on-line |
| **10/28/2003** | I.B.6. | Screening-Level Literature Review Findings message has been added. |

## VIII. Synonyms

Substance Name — Chlorodifluoromethane
CASRN — 75-45-6
Primary Synonym — HCFC-22
Last Revised — 10/01/1992

- 75-45-6
- Methane, chlorodifluoro-
- Chlorodifluoromethane
- Fluorocarbon 22
- Hydrochlorofluorocarbon 22
- Algeon 22
- ALGOFRENE TYPE 6
- Arcton 4
- CCRIS 858
- Chlorofluorocarbon 22
- Clorodifluometano [Spanish]
- Difluorochloromethane
- Difluoromonochloromethane
- ELECTRO-CF 22

- Eskimon 22
- F 22
- FC 22
- FC22
- FLUOROCARBON-22
- FREON
- Freon 22
- Frigen
- Frigen 22
- Genetron 22
- HSDB 143
- Isceon 22
- Isotron 22
- Khladon 22
- Monochlorodifluormethane
- Monochlorodifluoromethane
- Propellant 22
- R 22
- Refrigerant 22
- UCON 22
- HCFC-22