Concise International Chemical Assessment Document 23

2,2-DICHLORO-1,1,1-TRIFLUOROETHANE (HCFC-123)

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World Health Organization
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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based tolerable intakes and guidance values.

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

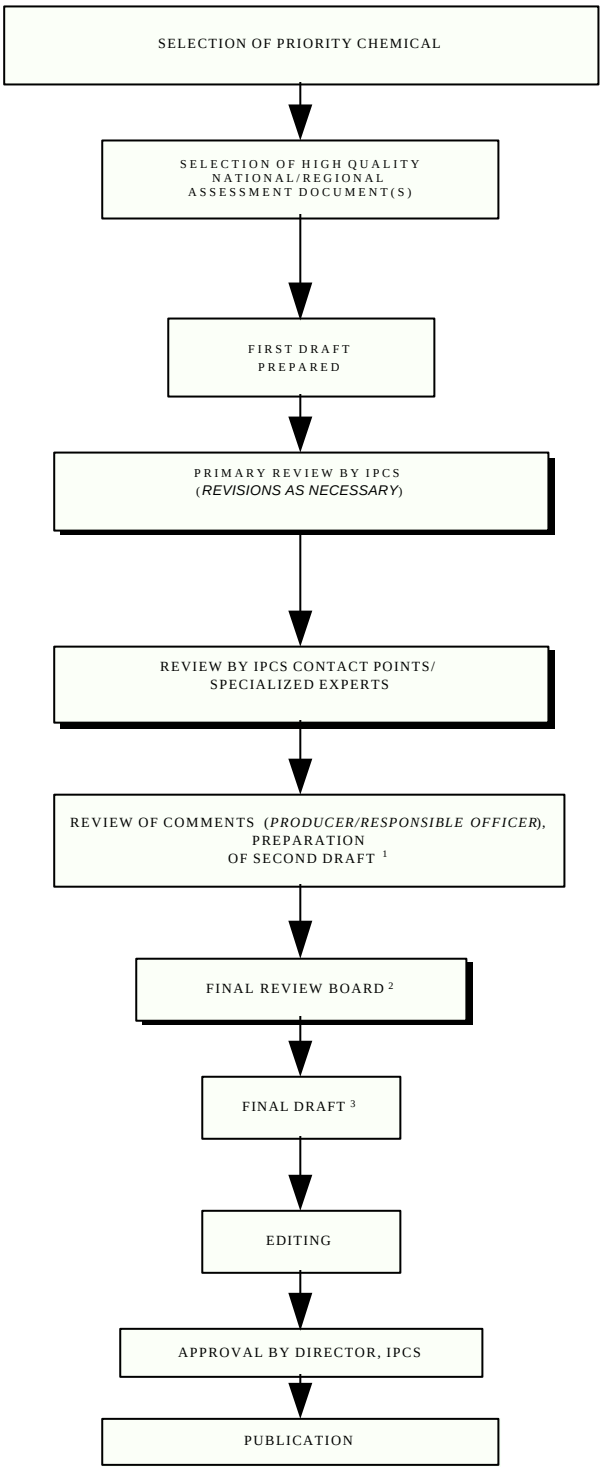
The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD was based principally on the assessments of the occupational health and environmental effects of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) completed under the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and published in March 1996 (NICNAS, 1996) and July 1999 (NICNAS, 1999). Relevant information that has become available since completion of the NICNAS reports or that was identified in a comprehensive search of several on-line databases up to August 1999 has also been assessed and included in this CICAD. This CICAD is an update of the review of HCFC-123 in the monograph Environmental Health Criteria 139 (IPCS, 1992), prompted by the advent of new and significant data. Information on the nature of the peer review and the availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. The CICAD was approved for publication at a meeting of the Final Review Board, held in Sydney, Australia, on 21–24 November 1999. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 1343) for 2,2-dichloro-1,1,1-trifluoroethane, produced by the International Programme on Chemical Safety, has been reproduced in Appendix 4 (IPCS, 1998).

HCFC-123 (CAS No. 306-83-2) is a synthetic, non-combustible, volatile liquid that is used as a refrigerant in commercial and industrial air-conditioning installations, in gaseous fire extinguishants, as a foam-blowing agent, and in metal and electronics cleaning. Its ozone-depleting potential is only 2% of that of CFC-11 (trichlorofluoromethane). It has a global warming potential of 300 over a 20-year time horizon relative to carbon dioxide. As such, HCFC-123 is currently used as a transitional replacement for chlorofluorocarbons and bromofluorocarbons phased out pursuant to the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer. The 1992 Copenhagen Amendment to the Montreal Protocol requires that HCFC-123 and other hydrochlorofluorocarbons be phased out by 2020.

Releases of HCFC-123 to the environment are primarily to ambient air. Although slightly toxic to fish, *Daphnia*, and algae, HCFC-123 is unlikely to pose a significant hazard to the aquatic environment, as it is not persistent in water, even at concentrations below the solubility limit. In the atmosphere, HCFC-123 has an estimated lifetime of less than 2 years. The main atmospheric breakdown product of HCFC-123 (and other, more widely used fluorocarbons) is trifluoroacetic acid, which will partition into aqueous phases in the environment. Although trifluoroacetic acid is resistant to degradation and may accumulate in certain closed aquatic systems, current and predicted concentrations from HCFC-123 emissions are below toxic thresholds.

Exposure of the general public to HCFC-123 is expected to be minimal. However, there is the potential for occupational exposure during the manufacture of HCFC-123 and the manufacture and use of products containing the chemical.

Limited information is available on the effects of HCFC-123 on humans. Cases of dizziness, headache, and nausea following a single exposure to unknown levels of airborne HCFC-123 have been reported, as well as cases of manifest or subclinical liver disease associated with repeated occupational exposures to HCFC-123 vapours at 5–1125 ppm (31.3–7030 mg/m^3) for 1–4 months.

The acute toxicity of HCFC-123 in laboratory animals is low. Inhalation for a few minutes to a few hours causes liver lesions in guinea-pigs at 1000 ppm (6.25 g/m^3), central nervous system (CNS) depression in all species examined at 5000 ppm (31.3 g/m^3), and adrenaline-induced cardiac arrhythmia in dogs at 20 000 ppm (125 g/m^3). In the rat and hamster, inhalation of more than 30 000 ppm (188 g/m^3) for 4 h causes severe CNS depression and death. HCFC-123 is not a skin irritant or sensitizer, but it can cause eye irritation in liquid form. In repeated-exposure inhalation toxicity studies lasting 2–39 weeks in rats, guinea-pigs, dogs, and monkeys, the main target organs were the liver, the hypothalamic-pituitary-gonadal endocrine system, and the CNS. The lowest-observed-adverse-effect level (LOAEL) based on liver effects was 30 ppm (188 mg/m^3). The no-observed-adverse-effect level (NOAEL) was 100 ppm (625 mg/m^3) based on endocrine effects and 300 ppm (1880 mg/m^3) based on CNS effects. There was no evidence that HCFC-123 is teratogenic in laboratory animals or induces reproductive or fetal toxicity at levels of exposure lower than those that cause other systemic effects. Growth was retarded in neonatal rats and monkeys reared by dams exposed to HCFC-123, with a LOAEL of 30 ppm (188 mg/m^3). The main metabolite of HCFC-123, trifluoroacetic acid, was found in the milk of the dams.

Although there was evidence of clastogenic activity in human lymphocytes exposed to HCFC-123 at high, cytotoxic concentrations *in vitro*, all other *in vitro* and *in vivo* tests for genetic toxicity were negative. Therefore, the evidence suggests that the chemical is unlikely to be genotoxic *in vivo*.

In a 2-year inhalation study in rats, there was an increased incidence of pre-cancerous lesions and benign

tumours in the liver, pancreas, and testes, but no exposure-related increase in the incidence of malignant tumours. It is likely that these tumours involve one or more non-genotoxic mechanisms, including peroxisome proliferation, hepatocellular damage, necrosis and regenerative proliferation, and disturbance of the hypothalamic-pituitary-testicular axis. Although humans may be less sensitive to tumours arising from some of these mechanisms, overall it is not possible to discount the tumours in an evaluation of the potential risk for humans.

The most relevant critical effects for a single, brief exposure to HCFC-123, such as from the discharge of a fire extinguishant, are CNS depression and an increased likelihood of adrenaline-induced cardiac arrhythmia. The most relevant critical effect from repeated exposure is liver lesions, which have been reported in workers exposed to air levels above 5 ppm (31.3 mg/m^3) for 1–4 months.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

HCFC-123 (CAS No. 306-83-2; $C_2HCl_2F_3$; 2,2-dichloro-1,1,1-trifluoroethane, 1,1,1-trifluoro-2,2-dichloroethane; see structural diagram in Figure 1) is a synthetic chemical that is a clear, colourless, non-combustible liquid with a slight ethereal odour. Other common names or abbreviations are FC 123, Fluorocarbon 123, Forane-123, Freon 123, Frigen, G 123, Genetron 123, R-123, and SUVA 123. HCFC-123 boils at 27.6 °C and is highly volatile, with a vapour pressure of 89.3 kPa at 25 °C. Its molecular weight is 152.93 g/mol. The solubility of HCFC-123 in water is 2.1 g/litre at 25 °C. The estimated log octanol/water partition coefficient is 2.3–2.9 (NICNAS, 1996). Its Henry's law constant has been measured at 2.6 m^3•kPa/mol at 22 °C (Chang & Criddle, 1995), corresponding to a dimensionless constant of 1.057. Additional physical/chemical properties are presented in the International Chemical Safety Card, reproduced in this document (Appendix 4).

The conversion factors for airborne HCFC-123 at 101.3 kPa and 25 °C are 1 ppm = 6.25 mg/m^3 and 1 mg/m^3 = 0.16 ppm.

3. ANALYTICAL METHODS

Methods of automated vapour detection include infrared absorption, infrared photo-acoustic, halide ion, and metallic oxide resistance sensors, with most systems having a detection limit of 1–2 ppm (6.25–12.5 mg/m^3) (Trane Company, 1991). Analysis for HCFC-123 in environmental media is usually by gas chromatography with flame ionization detection (Du Pont, 1993). This method has a detection limit of less than 0.94 ppm (5.88 mg/m^3).

There are no validated methods for biological monitoring of HCFC-123, although urinary excretion of trifluoroacetic acid has been used as an indicator of exposure (Tanaka et al., 1998).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

There are no known natural sources of HCFC-123. The principal use for HCFC-123 is as a refrigerant in commercial and industrial air-conditioning installations, in gaseous fire extinguishants, as a foam-blowing agent, and in metal and electronics cleaning. These uses are primarily as a temporary replacement for chlorofluorocarbons and bromofluorocarbons phased out pursuant to the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer. Worldwide, commercially available volumes of the chemical may reach 10 000 tonnes per year (AIHA, 1998). In countries that have ratified the Copenhagen Amendment to the Montreal Protocol, the manufacture, import, and export of HCFC-123 and other hydrochlorofluorocarbons will be phased out by 2020, although very small amounts will continue to be available until 2030 to service existing equipment. For information on the Montreal Protocol and subsequent amendments, see UNEP (1999).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

The majority of HCFC-123 released to the environment is in emissions to air — for example, from loss during normal running or maintenance of air-conditioning installations, from the discharge of fire extinguishants containing HCFC-123, or from the evaporation of solvents used in metal or electronics cleaning. Because of the limited solubility and high volatility of HCFC-123,

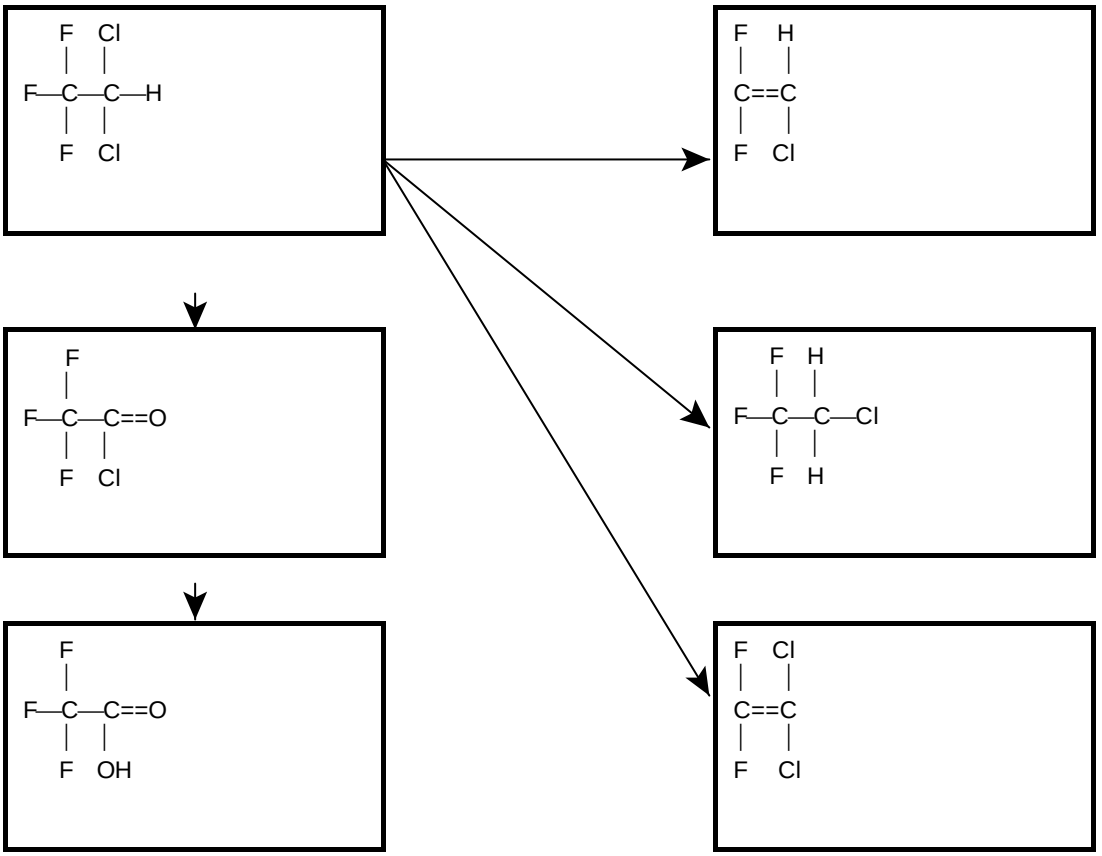


Figure 1: Structural formulas of HCFC-123 and metabolites.

only small amounts will enter aquatic environments. In a 28-day closed bottle test conducted according to Organisation for Economic Co-operation and Development (OECD) guidelines, oxygen consumption at a concentration of 12.5 mg HCFC-123/litre amounted to 24% of theoretical (Jenkins, 1992a); that is, HCFC-123 is not readily biodegradable, and spills to water would largely evaporate. HCFC-123 has been shown to undergo biodegradation in the presence of methanotrophic bacteria (Chang & Criddle, 1995). Microbial transformation involving reductive dechlorination to 2-chloro-1,1,1-trifluoroethane was observed in anoxic freshwater and salt-marsh sediments, whereas no degradation was observed in aerobic soils (Oremland et al., 1996). Although methanotrophic and anaerobic biodegradation may occur, they are unlikely to be effective removal mechanisms for this highly volatile chemical.

The estimated atmospheric lifetime of HCFC-123 is 1.4 years (WMO, 1995). HCFC-123 has an ozone-depleting potential of 0.02 relative to CFC-11 (trichlorofluoromethane). The global warming potential relative to carbon dioxide is 300, 93, and 29 over time horizons of 20, 100, and 500 years, respectively (WMO, 1995).

In the troposphere, HCFC-123 is attacked by hydroxyl radicals to form hydrogen chloride and trifluoroacetyl chloride (Hayman et al., 1994). The latter may undergo photolysis to carbon monoxide, carbon dioxide, hydrogen fluoride, and hydrogen chloride, but the major loss process is hydrolysis to trifluoroacetic acid by cloud water and precipitation in rain. Trifluoroacetic acid is also an atmospheric degradation product of other, more widely used fluorocarbons (Kotamarthi et al., 1998). It is very stable and may accumulate in certain closed aquatic systems. Reported environmental levels range from 30 to 3800 ng/litre in rain, snow, and fog and from 40 to 5400 ng/litre in most surface waters, with maximum concentrations of 6400 and 40 000 ng/litre in two desert lakes (Frank et al., 1996; Wujcik et al., 1998). The environmental fate of trifluoroacetic acid was reviewed by Boutonnet et al. (1999). The available evidence indicated that soil retention of trifluoroacetic acid is poor, particularly in soils with low levels of organic matter. Although biodegradation was observed under specific anaerobic conditions, the relevance of these findings was considered to be doubtful. Trifluoroacetic acid did not accumulate in lower aquatic life forms, such as bacteria, small invertebrates, oligochaete worms, and some aquatic plants, including duckweed. In terrestrial higher plants, trifluoroacetic acid appeared to be taken up with water and concentrated due to transpiration

water loss. The highest measured bioconcentration factor of 43 based on fresh weight was found in shoot/leaf from hydroponic wheat.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

HCFC-123 was detected in non-urban ambient air in Australia at levels less than 0.01 ppt (62.5 pg/m^3) (Fraser, 1994). Assuming that worldwide emissions will increase to 45 000 tonnes in 2010, the global average concentration of airborne HCFC-123 is projected to reach 1.1 ppt (7 ng/m^3) in that year, with levels being 2–4 times higher than the average near major sources of emissions in eastern North America and central Europe (Kotamarthi et al., 1998).

Information on levels of HCFC-123 in water, wildlife or food was not available.

6.2 Human exposure

HCFC-123 is not used in consumer products. Indirect exposure via the environment would be low, as the concentration in ambient air is less than 0.01 ppt (62.5 pg/m^3) and HCFC-123 is unlikely to persist in other media because of its limited solubility and high volatility. Therefore, exposure of the general population to HCFC-123 is expected to be minimal.

There is potential for occupational exposure, predominantly via inhalation, during the manufacture of HCFC-123 and the manufacture and use of products containing HCFC-123, such as the operation and maintenance of air-conditioning installations running on HCFC-123, the discharge of HCFC-123 from fire protection systems, and the use of liquid HCFC-123 in metal and electronics cleaning.

In an HCFC-123 manufacturing plant in Canada, two operators monitored over 165–480 min on 4 separate days had time-weighted breathing-zone levels of HCFC-123 ranging from 1.16 to 8.94 ppm (7.25 to 55.9 mg/m^3). On one occasion, a drum-filling lance failure resulted in a level in excess of 33 ppm (206 mg/m^3) (Du Pont, personal communication, 1999). No monitoring data were available for the manufacture of products containing HCFC-123.

Several studies have measured HCFC-123 levels in chiller machinery rooms during normal operations as well as maintenance and repair activities. In 4 of 12 unmanned machinery rooms containing air-conditioning equipment running on HCFC-123, air levels were below 1 ppm (6.25 mg/m^3) (4-h time-weighted average) at three sites (Trane Company, 1991). At one site, where samples were taken near a leak and a half-empty HCFC-123 drum, levels of 5.9–13.6 ppm (36.9–85.0 mg/m^3) (20-min time-weighted average) were recorded. At the rest of the sites, machinery room air levels were below the limit of detection (0.2–0.4 ppm [1.25–2.50 mg/m^3]). Breathing-zone levels of HCFC-123 during routine chiller maintenance operations, including refrigerant transfer, were measured at nine US installations. Two-hour to 12-h time-weighted average concentrations were less than 1 ppm (6.25 mg/m^3) in five cases, less than 2 ppm (12.5 mg/m^3) in three cases, and in the range of 2–5 ppm (12.5–31.3 mg/m^3) in one case (MRI, 1991; Sibley, 1992; Trane Company, 1992). In Australia, 4- to 6-h time-weighted average concentrations were less than 1 ppm (6.25 mg/m^3) during repair work at a single installation (NICNAS, 1996). In these studies, continuous area monitoring showed time-weighted average air concentrations below 1 ppm (6.25 mg/m^3), with activity-related instantaneous peaks ranging from 30 to 500 ppm (188 to 3130 mg/m^3).

Air levels resulting from the use of a fire extinguishant containing 93% HCFC-123 were measured during fire control exercises in which the firefighters wore a self-contained breathing apparatus (MRI, 1993a,b). Outdoor discharge resulted in maximum breathing-zone levels ranging from 7 to 870 ppm (43.8 to 5440 mg/m^3), depending on the type of fire hazard. Inside an aircraft hangar, the discharge of hand-held extinguishers resulted in a breathing-zone concentration of 20 ppm (125 mg/m^3) during discharge, with average static air levels ranging from 29 to 141 ppm (181 to 881 mg/m^3) over the next 30 min. With a large semi-portable fire extinguisher, breathing-zone concentrations during discharge reached 180–300 ppm (1130–1880 mg/m^3), whereas average static air levels ranged from 165 to 557 ppm (1030 to 3480 mg/m^3) over the next 30 min.

In a US factory converted to using HCFC-123 in its degreaser, personal air monitoring during normal degreaser operations showed 5.5-h time-weighted average levels of HCFC-123 that ranged from 5.3 to 12.0 ppm (33.1 to 75.0 mg/m^3) throughout the facility.[1] Charging and unloading the degreaser resulted in short-term breathing-zone levels ranging from 160 to 460 ppm (1000 to 2880 mg/m^3).

[1] AlliedSignal Inc., personal communication, 1998 [cited in NICNAS, 1999].

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

HCFC-123 is readily absorbed by inhalation and distributed throughout the body, where it reaches levels in body fat up to 25 times higher than those in blood (Vinegar et al., 1994). Following exposure to an initial concentration of 2000 ppm (12.5 g/m^3) radiolabelled HCFC-123 over two consecutive 3-h periods in a closed-chamber system, total uptake was 50–60% in rats and 90–100% in guinea-pigs (Urban & Dekant, 1994). In rats exposed to initial concentrations of 120–11 000 ppm (0.75–68.8 g/m^3) HCFC-123 for 6 h, the inhalation uptake showed a rapid distribution phase lasting 30–45 min followed by a slow linear uptake phase (Vinegar et al., 1994). Blood levels declined rapidly once exposure was terminated. In rats exposed to 1000 ppm (6.25 g/m^3), blood concentrations fell from 15.0 mg/litre at the end of a 4-h exposure period to 4.5 mg/litre at 4 min post-exposure and 1.5 mg/litre at 1 h post-exposure (Vinegar et al., 1994). After the initial decline, HCFC-123 concentrations in both blood and fat decreased log-linearly with a half-life of approximately 80 min, indicating fat as the main depository for unmetabolized HCFC-123. Experimentally determined tissue to air partition coefficients were 2–3 for gut and muscle, 3–4 for blood, 3–5 for liver, and 60–70 for fat (Dekant, 1993; Vinegar et al., 1994). Data on oral or dermal absorption were not available.

In the rat, 26–32% of the uptake of HCFC-123 is metabolized, predominantly by oxidation to trifluoroacetyl chloride, which is hydrolysed to trifluoroacetic acid or reacts with lysine residues in proteins or with low-molecular-weight amines to form *N*-trifluoroacetyl amides (Harris et al., 1992; Dodd et al., 1993; Urban & Dekant, 1994). Minor, reductive pathways lead to the formation of very small amounts of 2-chloro-1,1,1-trifluoroethane, 2-chloro-1,1-difluoroethene, and 2,2-dichloro-1,1-difluoroethene. The latter reacts with glutathione to form *N*-acetyl-*S*-(2,2-dichloro-1,1-difluoroethyl)-L-cysteine. The structures of these metabolites are shown in Figure 1. Both oxidation and reduction of HCFC-123 are catalysed by cytochrome P450 2E1 (CYP2E1). In human liver microsomes, the major biotransformation product is trifluoroacetic acid (Urban et al., 1994). Its rate of formation was directly related to the amount of CYP2E1 present and 1.5–16 times faster than the rate in rat microsomes.

In experimental animals, the major metabolite in blood, urine, and milk is trifluoroacetic acid. In rats exposed by inhalation to 1000 ppm (6.25 g/m^3) HCFC-123 for 4 h, blood levels of parent compound and trifluoroacetic acid amounted to 15.0 and 93.1 mg/litre, respectively (Vinegar et al., 1994). At 10 000 ppm (62.5 g/m^3), the corresponding concentrations were 93.5 and 37.8 mg/litre, respectively. Trifluoroacetic acid blood levels rebounded and peaked 12–26 h post-exposure, indicating that the metabolism of HCFC-123 is subject to substrate inhibition at exposures above 1000 ppm (6.25 g/m^3). For exposure levels below 2000 ppm (12.5 g/m^3), the metabolic rate constants developed for HCFC-123 were K_m = 1.2 mg/litre and V_{max} = 7.20 mg/kg body weight per hour for male rats and K_m = 1.2 mg/litre and V_{max} = 7.97 mg/kg body weight per hour for female rats (Loizou et al., 1994). Generally, HCFC-123 was not detected in blood samples collected within 1 h post-exposure from lactating rhesus monkeys exposed by inhalation to 1000 ppm (6.25 g/m^3) for 6 h per day, whereas trifluoroacetic acid concentrations reached 150–190 µg/ml after 2–3 weeks of exposure. Based on data from a single monkey, the half-life of trifluoroacetic acid in blood was approximately 24 h (Slauter, 1997). In rats and guinea-pigs exposed to ^{14}C-labelled HCFC-123 vapours for 6 h and sacrificed 48 h post-exposure, only low amounts of radioactivity remained in the organs examined (Urban & Dekant, 1994). The liver contained most of the radiolabel, followed by testes and kidneys, lungs, brain, pancreas, and spleen. Covalent binding of labelled material was highest in liver tissue (0.4–0.7 nmol/mg protein), followed by lungs, kidneys, and plasma (0.1–0.3 nmol/mg protein). Trifluoroacetylated tissue proteins have been detected by immunological techniques in the liver and at 20- to 200-fold lower levels in the kidney and heart of rats 6–12 h after exposure to HCFC-123 by inhalation or intraperitoneal injection (Harris et al., 1992; Huwyler & Gut, 1992; Huwyler et al., 1992).

The available data indicate that the predominant routes of HCFC-123 elimination are exhalation of the parent compound and urinary excretion of trifluoroacetic acid. In rats exposed to an initial concentration of 2000 ppm (12.5 g/m^3) radiolabelled HCFC-123 for two consecutive 3-h periods and sacrificed 48 h post-exposure, 23–28% of the radioactive uptake was eliminated in the urine, predominantly as trifluoroacetic acid, whereas 3–4% was recovered from the body (Urban & Dekant, 1994). Small amounts of minor metabolites, such as *N*-acetyl-*S*-(2,2-dichloro-1,1-difluoroethyl)-L-cysteine, *N*-trifluoroacetyl-2-aminoethanol, and fluoride ion, were recovered from urine, and trace amounts of 2-chloro-1,1,1-trifluoroethane were detected in expired air (Urban & Dekant, 1994; Vinegar et al., 1994). In lactating rats and monkeys exposed to 1000 ppm (6.25 g/m^3) HCFC-123 for 6 h per day for 3 weeks, trifluoroacetic acid was found in milk at a maximum concentration of 65 and 30 µg/ml, respectively (Buschman, 1996; Slauter, 1997). In monkeys, the milk also contained small amounts (up to

5 µg/ml) of HCFC-123. Rat milk was not analysed for HCFC-123, and neither monkey nor rat milk was analysed for metabolites other than trifluoroacetic acid.

An analogue of HCFC-123, the common inhalation anaesthetic halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), is also metabolized by hepatic CYP2E1 to trifluoroacetyl chloride, causing trifluoroacetylation of liver proteins (Harris et al., 1992; Urban et al., 1994). These include cytochrome P450 itself and other enzymes, many of which have been identified as residing in the lumen of the endoplasmic reticulum and involved in the maturation of newly synthesized proteins (Cohen et al., 1997). Both halothane and HCFC-123 induce peroxisome proliferation and increased $-oxidation in rat liver cells (Keller et al., 1998). They are also highly effective in inducing excess uncoupled cytochrome P450 activity in rabbit liver microsomes, thus increasing hepatic oxygen consumption and facilitating the oxidation of other cytochrome P450 substrates (Wang et al., 1993).

Only limited information was available on the kinetics and metabolism of HCFC-123 in humans *in vivo*. In four volunteers exposed by inhalation to 60–73 ppm (375–460 mg/m^3) HCFC-123 for 6 h, the concentration of trifluoroacetic acid in the urine peaked at 10–27 mg/litre by 20–30 h and returned to zero by 96 h post-exposure, indicating an elimination half-life of 25 h (Tanaka et al., 1998). Physiologically based pharmacokinetic models for halothane in humans and for halothane and HCFC-123 in rats have been used to deduce a human model for HCFC-123 and its main metabolite, trifluoroacetic acid (Williams et al., 1996). As the model has not been validated, its usefulness as a predictive tool is unknown at this time.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

Unless otherwise indicated, only effects that were statistically different ($P < 0.05$) from controls have been considered. All inhalation studies were performed by whole-body exposure, unless otherwise mentioned.

8.1 Single exposure

When HCFC-123 was administered in corn oil by oral gavage to rats at doses ranging from 2.25 to 11 g/kg body weight, rapid respiration and prostration were recorded at and above 3.4 g/kg body weight. An LD_{50} was not determined. The lowest dose causing mortality was 9 g/kg body weight (Henry, 1975).

In the rat and the hamster, inhalation of more than 30 000 ppm (188 g/m^3) caused severe CNS depression and death (Clayton, 1966; Hall & Moore, 1975; Coate, 1976; Darr, 1981). The 4-h LC_{50} ranged from 28 400 to 52 600 ppm (178–329 g/m^3). Clinical signs of toxicity included sedation, loss of muscle coordination and balance, prostration, and dyspnoea. Gross pathological findings were either negative or limited to congestion or discoloration of the lungs, kidneys, liver, thymus, or small intestine. The lowest concentration causing reversible CNS depression (failures in unconditioned reflexes) in rats was 5000 ppm (31.3 g/m^3) (Mullin, 1976). In a study of cardiac sensitization to adrenaline, life-threatening or fatal arrhythmias occurred in 0 of 3, 4 of 6, and 3 of 3 dogs exposed nose-only to 10 000, 20 000, or 40 000 ppm (62.5, 125, or 250 g/m^3). The dogs were pretreated with intravenous adrenaline (8 µg/kg body weight) prior to exposure and challenged with an identical adrenaline dose after breathing the compound for 5 min. Based on these findings, an EC_{50} (5 min) of 19 000 ppm (119 g/m^3) and a NOAEL of 10 000 ppm (62.5 g/m^3) were determined (Trochimowicz & Mullin, 1973). Exposure of guinea-pigs to 1000–30 000 ppm (6.25–188 g/m^3) HCFC-123 for 4 h produced non-fatal liver damage in all exposure groups (Marit et al., 1994). At 48 h post-exposure, the liver effects included centrilobular vacuolar (fatty) change, multifocal random and centrilobular hepatocellular degeneration and necrosis, and increased levels of plasma isocitrate dehydrogenase, alanine transaminase (ALT), and aspartate transaminase (AST). In another study in guinea-pigs exposed to 10 000 ppm (62.5 g/m^3) for 4 h, liver injury was minimal unless the animals had been glutathione depleted prior to exposure (Lind et al., 1995).

In a rat and rabbit test for dermal toxicity carried out according to OECD guidelines, the only effect observed after a dose of 2000 mg liquid HCFC-123/kg body weight was applied under occlusion for 24 h was a slight to moderate erythema in 6 of 10 rabbits up to 5 days post-treatment. As such, the dermal LD_{50} for rats and rabbits was greater than 2000 mg/kg body weight (Brock, 1988a,b).

8.2 Irritation and sensitization

Application under occlusion of 0.5 ml liquid HCFC-123 for 4 h caused no erythema or oedema in a test for skin irritation potential in rabbits conducted according to OECD guidelines (Brock, 1988c). In rabbits, 0.1 ml undiluted HCFC-123 or 0.2 ml of a 50% solution in propylene glycol caused mild to moderate, reversible eye damage, including conjunctival irritation and corneal opacity (scoring not reported) (Britelli, 1975). HCFC-123 did not produce skin sensitization in guinea-pigs when

0.1 ml of a 1% solution in dimethyl phthalate was administered intradermally once a week for 3 weeks, followed by challenge 2 weeks later with 7 or 35 mg HCFC-123 dissolved in propylene glycol (Goodman, 1975).

8.3 Short-term exposure

In rats exposed to 1000, 5000, 10 000, or 20 000 ppm (6.25, 31.3, 62.5, or 125 g/m^3) HCFC-123 for 6 h per day, 5 days per week, in a 28-day inhalation toxicity study conducted in accordance with OECD guidelines, exposures to 5000 ppm (31.3 g/m^3) and above resulted in dose-related narcotic effects, which were reversible overnight (Kelly, 1989; Rusch et al., 1994). Body weight was reduced at all dose levels in females (8–10%) and at the two highest dose levels in males (14–15%). There was a dose-related increase in relative liver weight at all exposure levels in females (14–27%) and at the highest level in males (18%). Plasma levels of ALT and AST were increased by 35% and 71%, respectively, at the highest level in males. Except for isolated cases of fatty change at all dose levels, gross or microscopic liver lesions were not observed. A NOAEL was not established in this study.

In a study in male rats exposed to approximately 1000, 5000, or 20 000 ppm (6.25, 31.3, or 125 g/m^3) HCFC-123 for 6 h per day, 5 days per week, for 28 days, there was a decrease in body weight (6–11%) and an increase in relative testis weight (12–30%) in all dose groups and a 25% increase in relative liver weight in the highest dose group (Lewis, 1990). Microscopic liver lesions including dose-related hepatocyte hypertrophy and centrilobular fatty change were seen at all exposure levels, with proliferation of peroxisomes and mitochondria in liver cells of animals exposed to 5000 ppm (31.3 g/m^3) and above. Plasma levels of ALT, AST, and alkaline phosphatase (ALP) were increased by up to 79%, whereas plasma triglycerides and cholesterol were decreased by up to 70%, with AST and triglycerides being the most sensitive markers of hepatic injury.

Similar findings accompanied by a 3-fold increase in hepatocyte mitotic activity were reported from a study in which male rats were exposed to 18 200 ppm (114 g/m^3) HCFC-123 for 6 h per day, 5 days per week, for 28 days (Warheit, 1993). This study also found exposure-related testicular lesions, including germinal cell necrosis and atrophy of the seminiferous tubules. In male guinea-pigs exposed to 9400 ppm (58.8 g/m^3) HCFC-123 for 6 h per day, 5 days per week, for 28 days, there was evidence of microscopic liver lesions, including centrilobular vacuolar (fatty) change and hepatocellular necrosis, but no testicular effects were observed (Warheit, 1993).

8.4 Long-term exposure

8.4.1 Subchronic exposure

A number of subchronic inhalation studies have been carried out in rats and dogs and are summarized in Table 1. In each case, HCFC-123 was administered for 6 h per day, 5 days per week. The main effects were liver injury, with changes in liver-related clinical chemistry parameters occurring at 300 ppm (1.88 g/m^3) in rats and at 1000 ppm (6.25 g/m^3) in dogs, and CNS depression, with a reduction in arousal occurring at 1000 ppm (6.25 g/m^3) in rats.

8.4.2 Chronic exposure and carcinogenicity

In a 2-year inhalation study, groups of 80 male and female Sprague-Dawley rats were exposed for 6 h per day for 5 days per week to 300, 1000, or 5000 ppm (1.88, 6.25, or 31.3 g/m^3) HCFC-123 (Malley, 1992; Malley et al., 1995).

During the first year, rats exposed to 5000 ppm (31.3 g/m^3) appeared sedated, but quickly recovered after the daily exposures ended. Female rats exposed to 1000 ppm (6.25 g/m^3) and males and females exposed to 5000 ppm (31.3 g/m^3) had lower body weight and body weight gain. At the 12-month sacrifice, the relative liver weight in male and female rats exposed to 5000 ppm (31.3 g/m^3) was increased by 12% and 24%, respectively. No exposure-related gross or histopathological changes were observed. In both sexes, serum triglycerides and glucose were decreased at all exposure levels in a dose-related manner, by 65–100% and 15–31% for males and females, respectively. Serum cholesterol was decreased by approximately 30% in all exposed females and by 43% in males exposed to 5000 ppm (31.3 g/m^3).

During the second year of exposure, slight, reversible CNS depression continued to be observed at 5000 ppm (31.3 g/m^3). At the end of the 2-year period, there was a dose-related increase in survival rate, which reached a statistically significant level of 47% and 59% in females exposed to 1000 or 5000 ppm (6.25 or 31.3 g/m^3), respectively. This is an expected effect of chemicals that reduce body fat and blood lipids. Compared with the controls, body weight was decreased by 8% in females exposed to 1000 ppm (6.25 g/m^3) and by 12% in males and 21% in females exposed to 5000 ppm (31.3 g/m^3). At 5000 ppm (31.3 g/m^3), relative liver weight and the incidence of enlarged and discoloured livers were increased in males, as were grossly observed liver masses in females.

There were no exposure-related effects on the incidence of malignant tumours. There was an increase in hepatocellular adenomas in females and males, an

Table 1: Summary of effect levels in subchronic inhalation toxicity studies.

Species	Study design	Effects	Effect levels	Reference
Rats, albino, 35 males and 25 females per group	Exposed to 0, 500, 1000, or 5000 ppm (0, 3.13, 6.25, or 31.3 g/m^3) HCFC-123 for 90 days, with a 30-day recovery period.	Body weight marginally decreased in females at 1000 ppm and in both sexes at 5000 ppm. Kidney weight increased in all male test groups and in females at 5000 ppm (% change not reported). Relative liver weight increased in females at all exposure levels and in males at 5000 ppm (% change not reported). Microscopic liver lesions included mild focal necrosis in males from all test groups and minimal bile duct proliferation in males at 5000 ppm. At end of recovery period, there were no exposure-related body or organ weight changes or histopathological findings.	LOAEL = 500 ppm (3.13 g/m^3)	Industrial Bio-Test Laboratories, 1977; Rusch et al., 1994
Rats, Sprague-Dawley, 27 per sex per group	Exposed to 0, 1000, or 10 000 ppm (0, 6.25, or 62.5 g/m^3) HCFC-123 for 90 days. Histopatho-logical examination performed on 6 animals per group.	Reversible motor incoordination and unresponsiveness to noise at 10 000 ppm. Reduced body weight (8–17%) and increased relative liver weight (% change not reported) in both test groups. No exposure-related gross or histopathological findings. Elevated levels of AST in males at both exposure levels, ALT in males at 1000 ppm, and blood urea nitrogen (BUN) in males at both exposure levels and in females at 1000 ppm; glucose decreased in females in both test groups and in males at 10 000 ppm (% change not reported).	LOAEL = 1000 ppm (6.25 g/m^3)	Doleba-Crowe, 1978; Rusch et al., 1994
Rats, Sprague-Dawley, 10 per sex per group	Exposed to 0, 300, 1000, or 5000 ppm (0, 1.88, 6.25, or 31.3 g/m^3) HCFC-123 for 90 days.	Reduced responsiveness to auditory stimuli at 1000 and 5000 ppm. Relative liver weight increased by 12–17% and 19–22%, respectively, at 1000 and 5000 ppm. No exposure-related gross or histopathological findings. Dose-dependent elevations of AST, ALT, lactate dehydrogenase (LDH) in males at 1000 and 5000 ppm and BUN in females in all test groups and in males at 1000 and 5000 ppm. Triglycerides and glucose markedly decreased and hepatic $-oxidation activity increased 2- to 4-fold in all test groups. Dose-dependent decrease in cholesterol in females at 1000 and 5000 ppm.	LOAEL = 300 ppm (1.88 g/m^3)	Malley, 1990; Rusch et al., 1994
Rats, Sprague-Dawley, 10 per sex per group	Exposed to 0, 300, 1000, or 5000 ppm (0, 1.88, 6.25, or 31.3 g/m^3) HCFC-123 for 90 days, with a 28-day recovery period. Histological examinations limited to nervous tissues.	Reversible reduction in arousal at 1000 and 5000 ppm. No exposure-related gross or histopathological findings in cerebrum, medulla/pons, cerebellar cortex, spinal cord, ganglia, dorsal and ventral root fibres, or peripheral nerves.	NOAEL = 300 ppm (1.88 g/m^3)	Coombs, 1994
Dogs, beagles, 4 males per group	Exposed to 0, 1000, or 10 000 ppm (0, 6.25, or 62.5 g/m^3) HCFC-123 for 90 days.	Reversible motor incoordination and unresponsiveness at 10 000 ppm. At 10 000 ppm, discoloured livers with hepatocyte hypertrophy and necrosis with inflammatory cell infiltration. Elevated levels of ALP in both test groups and of BUN at 10 000 ppm (% change not reported).	LOAEL = 1000 ppm (6.25 g/m^3)	Doleba-Crowe, 1978; Rusch et al., 1994

increase in cholangiofibromas in high-dose females, a dose-related increase in pancreatic acinar cell adenomas in males, and an increase in Leydig (interstitial) cell adenomas in males at all dose levels (Table 2). Except for hepatocellular adenomas in males, the increase in the incidence of these tumours remained statistically significant when corrected for mortality. Historical data on tumour incidence in the strain used for this study were not available. Other exposure-related lesions included hepatic foci of cellular alteration and focal pancreatic acinar cell hyperplasia (lesions less than 3 mm in diameter) in males and females at 1000 and 5000 ppm (6.25 and 31.3 g/m^3), in addition to hepatic focal necrosis in males, cholangiofibrosis in females, and hepatic centrilobular fatty change in both sexes at 5000 ppm (31.3 g/m^3). Dose-related focal Leydig cell hyperplasia (lesions less than the diameter of three adjacent tubules) was observed in male rats exposed to 1000 and 5000 ppm (6.25 and 31.3 g/m^3). The incidence of diffuse retinal atrophy was increased in both sexes at all exposure levels. Serum triglycerides and cholesterol continued to be decreased in both sexes by 46–75% and 31–48%, respectively.

As there were changes in clinical chemistry parameters and an increased incidence of hepatocellular and Leydig cell adenomas at the lowest dose tested (300 ppm [1.88 g/m^3]), a NOAEL was not established in this study.

Table 2: Incidence of selected non-neoplastic and neoplastic lesions in the liver, pancreas, and testes in the 2-year rat inhalation study.[a,b]

	Incidence of lesions			
	0 ppm	300 ppm	1000 ppm	5000 ppm
Male				
Liver				
Hepatocellular adenoma	3/67	2/66	2/66	8/66[c]
Basophilic foci of alteration	8/67	10/66	20/66[d]	30/66[d]
Clear cell foci of alteration	8/67	9/66	30/66[d]	19/66[d]
Mixed foci of alteration	3/67	6/66	6/66	12/66[d]
Eosinophilic foci of alteration	8/67	16/66	18/66[d]	13/66
Cholangiofibroma	0/67	0/66	0/66	0/66
Cholangiofibrosis	0/67	0/66	0/66	0/66
Pancreas				
Acinar cell adenoma	1/67	4/66	12/64[e]	14/66[e]
Focal acinar cell hyperplasia	5/67	6/66	13/64[d]	19/66[d]
Testes				
Leydig cell adenoma	4/67	12/66[f]	9/66[f]	14/66[f]
Leydig cell hyperplasia	8/67	15/66	23/66[d]	30/66[d]
Female				
Liver				
Hepatocellular adenoma	0/65	5/67[e]	2/67	7/69[e]
Basophilic foci of alteration	17/65	26/67	32/67[d]	46/69[d]
Clear cell foci of alteration	14/65	7/67	16/67	15/69
Mixed foci of alteration	2/65	3/67	13/67[d]	22/69[d]
Eosinophilic foci of alteration	8/65	11/67	22/67	30/69[d]
Cholangiofibroma	0/65	0/67	0/67	6/69[e]
Cholangiofibrosis	0/65	0/67	0/67	9/69[d]
Pancreas				
Acinar cell adenoma	0/65	2/66	0/67	2/69
Focal acinar cell hyperplasia	0/65	4/66	6/67[d]	8/69[d]

[a] From Malley (1992); Malley et al. (1995).

[b] Only lesions whose incidence attained statistical significance in at least one male or female dose group are included in the table. Other non-statistically significant lesions are discussed in the text. The figures give the number of lesions per number of tissues available for histological examination. A few animals and tissues were lost due to autolysis.

[c] $P < 0.05$ (Cochran-Armitage test for trend).

[d] $P < 0.05$ (Fisher's exact test compared with controls).

[e] $P < 0.05$ (Cochran-Armitage test for trend and 2/2 tests for mortality-adjusted statistical analysis).

[f] $P < 0.05$ (Cochran-Armitage test for trend and 1/2 tests for mortality-adjusted statistical analysis).

8.5 Genotoxicity and related end-points

HCFC-123 was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1525, TA1537, or TA1538 with or without metabolic activation, even at concentrations of 750 mg per vessel or 150 000 ppm (938 g/m^3), which were clearly toxic (Callander, 1989). HCFC-123 was found to be clastogenic in two separate studies in human lymphocytes *in vitro*, both with and without metabolic activation, at relatively high concentrations that also reduced the mitotic rate (Table 3). It was also noted to be clastogenic in the absence, but not in the presence, of a metabolic activation system in human lymphocytes exposed to the chemical at 500 µg/ml; further details were not available (ICI, 1992). No transformation to anchorage-independent cells was observed when HCFC-123 was tested in baby hamster kidney fibroblasts (BHK21 cells) with and without metabolic activation (Longstaff et al., 1984).

In vivo, a test for chromosome aberrations in the lymphocytes of rats exposed by inhalation to up to 5000 ppm (31.3 g/m^3) HCFC-123 for 6 h per day, 5 days a week, for 2 weeks was negative (Marshal, 1992), although the failure to induce signs of cytotoxicity cast doubt on the validity of this finding. No increase was

Table 3: Chromosome aberrations in human lymphocytes *in vitro.*

Physical form of HCFC-123	Exposure protocol[a]	Concentration[b]	Mean mitotic index	Number of cells with aberrations (excluding gaps)	Reference
Liquid	3-h exposure (without S9)	0 µg/ml	25.2	1	Dance, 1991
		73 µg/ml	19.6	2	
		146 µg/ml	21.7	3	
		292 µg/ml	21.1	3	
		CBC (2 µg/ml)	14.0	91	
	3-h exposure (with S9)	0 µg/ml	23.8	1	
		146 µg/ml	21.8	2	
		292 µg/ml	14.7	6	
		584 µg/ml	6.6	5	
		CP (6 µg/ml)	8.4	106	
	24-h exposure (without S9)	0 µg/ml	30.7	2	
		36 µg/ml	27.4	3	
		73 µg/ml	21.5	10[c]	
		292 µg/ml	9.7	31[d]	
		CBC (2 µg/ml)	22.9	70	
Vapour	3-h exposure (without S9)	0 ppm	24.9	1	Edwards, 1991
		75 000 ppm	23.9	3	
		150 000 ppm	17.9	0[e]	
		300 000 ppm	10.3	5[e]	
		CBC (2 µg/ml)	18.5	60	
	3-h exposure (with S9)	0 ppm	22.2	4	
		75 000 ppm	24.1	3	
		150 000 ppm	21.0	4	
		300 000 ppm	9.5	23[e,f]	
		CP (6 µg/ml)	15.2	107	
	24-h exposure (without S9)	0 ppm	16.6	1	
		25 000 ppm	19.1	9[d]	
		50 000 ppm	13.2	18[f]	
		100 000 ppm	5.9	24[f]	
		CBC (2 µg/ml)	13.5	118	

[a] S9 = metabolic activation system.
[b] Positive controls: CBC = chlorambucil; CP = cyclophosphamide.
[c] $P < 0.05$.
[d] $P < 0.01$.
[e] Increase in number of polyploid cells.
[f] $P < 0.001$.

found in the incidence of micronuclei or in the ratio of polychromatic to normochromatic erythrocytes in a micronucleus test in mice exposed nose-only to up to 18 000 ppm (113 g/m^3) HCFC-123 for 6 h (Muller & Hofmann, 1988). In the livers of rats exposed to 12 500 or 20 000 ppm (78.1 or 125 g/m^3) HCFC-123 for 6 h, neither net nuclear grain count nor percentage cells in repair showed any evidence of unscheduled DNA synthesis (Kennelly, 1993).

Although HCFC-123 was clastogenic *in vitro* at high concentrations, all other *in vitro* and *in vivo* tests for genetic toxicity were negative. Overall, the available studies suggest that HCFC-123 is unlikely to be genotoxic *in vivo.*

8.6 Reproductive and developmental toxicity

In studies conducted according to OECD guidelines, HCFC-123 was neither embryotoxic nor teratogenic in pregnant rats exposed for 6 h per day on days 6–15 of gestation by inhalation to 0, 5000, or 10 000 ppm (0, 31.3, or 62.5 g/m^3) HCFC-123, although maternal toxicity in the

form of reduced weight gain and CNS depression were observed at both exposure levels (Culik & Kelly, 1976; Brewer & Smith, 1977). In a range-finding study in which fetal examinations were limited to external structural abnormalities, HCFC-123 was not embryotoxic or teratogenic in pregnant rabbits exposed for 6 h per day on days 6–18 of gestation by inhalation to 0, 500, 1500, or 5000 ppm (0, 3.13, 9.38, or 31.3 g/m^3) HCFC-123, although dose-related maternal toxicity characterized by reduced weight gain and food consumption was evident at all exposure levels (Malinverno et al., 1996).

In a two-generation reproductive toxicity study in Sprague-Dawley rats conducted in accordance with OECD guidelines, male and female animals were exposed for 6 h per day, 7 days a week, by inhalation to 0, 30, 100, 300, or 1000 ppm (0, 0.188, 0.625, 1.88, or 6.25 g/m^3) HCFC-123 (Hughes, 1994; Malinverno et al., 1996). The F_0 (parental generation) animals were exposed from 6 weeks of age for 23–39 weeks, including a 2-week mating period, the gestation period, and, except for maternal animals on postpartum days 0–4, until the offspring were weaned. The F_1 generation was exposed from 4 weeks of age through to weaning of their litters (F_2 generation), for a total of approximately 28 weeks.

The only adverse reproductive effect was a 17% decrease in implantation count among F_1 females at the highest exposure level. In terms of development, pup growth was impaired during the pre-weaning period when exposure was confined to the lactating parent female. In the F_1 generation, mean pup weight was decreased by approximately 10% at exposures at and above 100 ppm (0.625 g/m^3), whereas mean pup weight in F_1 offspring (F_2 generation) was decreased by approximately 20% at all exposure levels. In adult rats, retarded weight gain was observed at 100 ppm (0.625 g/m^3) and above in F_0 animals and at 300 ppm (1.88 g/m^3) and above in the F_1 generation. There was a dose-dependent, 8–39% increase in liver weight in all exposed F_0 groups and an 8–10% increase at 100 ppm (0.625 g/m^3) and above in F_1 animals. In F_1 animals exposed to HCFC-123 for approximately 28 weeks, exposure-related histopathological changes were confined to a dose-related increase in the incidence of centrilobular hepatocyte enlargement and in the incidence and degree of hepatocyte vacuolation at 300 ppm (1.88 g/m^3) and above. No microscopic changes were detected in the livers of F_2 weanling rats from the 1000 ppm (6.25 g/m^3) exposure group. In both generations, there was a decrease in serum triglycerides in both sexes, whereas serum cholesterol was increased in males and decreased in females. Levels of ALT, AST, or other liver enzymes were not determined. Male rats exposed at or above 300 ppm (1.88 g/m^3) had increased plasma levels of luteinizing hormone (LH) after 10 weeks of exposure, which had reverted to normal at week 38. In this study, the NOAEL, based on effects on fertility, was 300 ppm (1.88 g/m^3). The LOAEL, based on developmental effects (retarded neonatal growth during lactation) and on increased liver weight and changes in liver-related clinical chemistry parameters, was 30 ppm (0.188 g/m^3).

After 22 weeks of exposure, a sample of F_1 male rats was drawn from the two-generation reproductive toxicity study for endocrinological investigations (Sandow et al., 1995b). In 10 males from each exposure group, serum levels of LH and testosterone were determined before and after an injection of LH releasing hormone. The testes of another eight males per group were incubated *in vitro* with human chorionic gonadotropin (which stimulates steroid hormone biosynthesis). The incubation medium and testis tissue were analysed for content of testosterone, progesterone, estradiol-17-$, 17"-OH-progesterone, and)-4-androstenedione. Basal serum LH and testosterone levels were similar to those of controls. However, after stimulation with LH releasing hormone, the LH in rats exposed to 300 ppm (1.88 g/m^3) was 32% lower than in controls; at 1000 ppm (6.25 g/m^3), LH was 39% and testosterone 46% lower than in the control group. In the *ex vivo* test, HCFC-123 inhalation did not affect the secretory capacity for steroid hormones or alter the content of these hormones in the testes at the end of the incubation period, except for a slight reduction of)-4-androstenedione at 1000 ppm (6.25 g/m^3).

In an endocrinological study in rats of both sexes, exposure to 5200 ppm (32.5 g/m^3) HCFC-123 for 6 h per day (similar to the highest dose level in the 2-year bioassay) for 14 consecutive days was associated with sedation, decreased body, kidney, ovary, and pituitary weights in females, and increased relative liver weight in males (Hofmann, 1995; Sandow et al., 1995a). In males, the prolactin response after monoiodotyrosine stimulation, the testosterone response after stimulation with buserelin (a synthetic gonadotropin releasing hormone), and the testicular testosterone content were all reduced by approximately 50%. In females, the gonadotropin response to buserelin stimulation was enhanced and the pituitary content of follicle stimulating hormone and prolactin was reduced, in both cases by approximately 50%.

These endocrinological investigations indicate that HCFC-123 has little, if any, effect on steroid production in rat testes, but impairs the prolactin, LH, and testosterone response to pituitary stimulants. The NOAEL based on this effect was 100 ppm (0.625 g/m^3).

A lactation study was conducted in groups of pregnant and lactating Sprague-Dawley (Crl:CD BR) rats exposed to 0 or 1000 ppm (0 or 6.25 g/m^3) HCFC-123 for 6

h per day on days 5–19 of gestation and on days 5–21 postpartum (Buschman, 1996). Within 2 days of birth, litters were crossed over between dams to create four groups comprising exposed or control dams rearing litters from different exposed or control mothers. Absolute and relative liver weights were increased and serum triglycerides, cholesterol, and glucose decreased in dams exposed to HCFC-123. The milk of dams exposed to HCFC-123 was of normal quantity and quality (with regard to content of protein, lactose, and fat) but contained trifluoroacetic acid at an average concentration of 50 µg/ml. Trifluoroacetic acid was also found in the urine of pups reared by dams exposed to HCFC-123. There were no differences in absolute or relative liver weight or any abnormal clinical signs or gross findings in any of the groups of pups, but pups reared by dams exposed to HCFC-123 had a 10% lower growth rate and decreased serum triglycerides compared with pups reared by non-exposed dams. Before cross-over, there was no difference between groups with respect to mean pup and litter weight. As such, these findings indicate that the retarded neonatal growth observed in the two-generation reproductive toxicity study was due to factors in the milk of exposed mothers, probably trifluoroacetic acid, rather than to exposure *in utero*.

When groups of four lactating rhesus monkeys and their neonates were exposed to either 0 or 1000 ppm (0 or 6.25 g/m^3) HCFC-123 for 6 h per day for 21–22 consecutive days, there were no effects on maternal body weight, serum triglycerides, cholesterol, and glucose, or milk composition (Slauter, 1997). Liver biopsy specimens taken from the mothers at the end of the study revealed exposure-related lesions, including mild to moderate centrilobular hepatocyte vacuolation, trace to moderate centrilobular hepatocyte necrosis, and trace to mild subacute inflammation. As a rule, HCFC-123 was not detected in the blood of mothers or neonates, whereas trifluoroacetic acid was present at concentrations of 9–70 µg/ml in exposed mothers and of 17–190 µg/ml in neonates, with individual blood levels being 2–6 times higher in the neonates than in their corresponding mothers. Milk from exposed mothers contained HCFC-123 and trifluoroacetic acid at concentrations of 1–5 µg/ml and 17–30 µg/ml, respectively. Although no statistical analysis was attempted because of the small number of observations, the average growth rate was 10% lower in exposed neonates than in unexposed controls.

9. EFFECTS ON HUMANS

The available data on the human health effects of HCFC-123 were limited to a single case report of dizziness, headache, and nausea in workers exposed to unknown levels of the chemical following the rupture of an industrial chiller[1] and three case reports of hepatic effects involving 26 workers following repeated exposure to HCFC-123 vapours.

Nine cases of liver effects were reported in gantry drivers at a smelting depot in Belgium (Hoet et al., 1997). They occurred 1–4 months after the refrigerant utilized in the crane cabin air-conditioning system had been replaced by a blend containing 57% HCFC-123, 40% HCFC-124 (1-chloro-1,2,2,2-tetrafluoroethane), and 3% propane.[2] One driver admitted to hospital was found to have increased levels of AST, ALT, ALP, (-glutamyl transferase, and total and conjugated bilirubin and decreased prothrombin activity, with AST and ALT levels being 15–23 times above the upper limit of the normal range. Autoimmune, viral, and drug- or alcohol-induced hepatitis were ruled out. A liver biopsy showed focal liver cell necrosis, plugging of bile ducts, and the presence of trifluoroacetylated proteins. The symptoms regressed during the period of non-exposure but recurred when the driver returned to work 2 months later. Eight other drivers showed signs of varying degrees of liver abnormalities. Serum antibodies to human liver enzymes (CYP2E1 and/or protein disulfide isomerase isoform P58) were detected in five of six cases examined. A workplace inspection revealed that the plastic pipes of the air-conditioning system were perforated and that refrigerant was leaking into the crane cabin. No further cases occurred after the system was repaired. Although the workers were exposed to both HCFC-123 and HCFC-124, the latter is unlikely to have contributed to the observed effects, as the NOAEL for HCFC-124 was 50 000 ppm (280 g/m^3) in a 90-day inhalation toxicity study in rats (Malley et al., 1996), whereas the LOAEL for HCFC-123 in a similar study in the same strain and laboratory was 300 ppm (1.88 g/m^3) (Table 1).

Eight cases of liver effects were reported in workers exposed to the vapours of a solvent degreaser containing HCFC-123.[3] Two months after a US factory converted to using HCFC-123 in its degreaser, two employees who worked closely with the degreaser were found to have liver disease. They had elevated blood levels of liver enzymes, particularly ALT (32–56 times above the upper limit of the normal range) and AST (14–33 times above the upper limit of the normal range), had elevated total and conjugated bilirubin, and tested

[1] Carrier Canada Ltd, personal communication, 1993 [cited in NICNAS, 1996].

[2] N. Verlinden, personal communication, 1997 [cited in NICNAS, 1999].

[3] AlliedSignal Inc., personal communication, 1998 [cited in NICNAS, 1999].

Table 4: Summary of effects of HCFC-123 in aquatic organisms.

Test	Species	Effects and effect levels	Comments	Reference
Acute toxicity (96 h), flow-through conditions	Fathead minnow (*Pimephales promelas*)	Lethargy LC_{50} > 76 mg/litre (measured)	Rapid degassing of HCFC-123 from test solutions	Pierson, 1990a
Acute toxicity (96 h), static conditions	Rainbow trout (*Oncorhynchus mykiss*)	Lethargy, darkened pigmentation at 15 mg/litre and above LC_{50} = 56 mg/litre (measured)		Jenkins, 1992b
Immobilization (48 h), static conditions	*Daphnia magna*	Lethargy EC_{50} = 17 mg/litre (measured)		Jenkins, 1992c
Immobilization (48 h), static conditions	*Daphnia magna*	Lethargy EC_{50} = 45.8 mg/litre (nominal)	Measured concentrations #75% of nominal	Pierson, 1990b
Algal growth inhibition (96 h), static conditions	*Selenastrum capricornutum*	EC_{50} = 68 mg/litre (measured)	Based on biomass integral	Jenkins, 1992d

negative for viral hepatitis. Subsequent testing of all 27 factory employees revealed four additional cases of elevated liver enzymes. When retested 1 month later but before the use of HCFC-123 was discontinued, five of the affected employees had improved markedly, whereas one had deteriorated, and there was one new case with slightly elevated ALT and AST levels. All in all, liver enzymes were elevated in 3 of 4 employees who worked with the degreaser and in 4 of 23 workers who did not. Air monitoring was conducted when HCFC-123 use began and again shortly after the first cases were diagnosed. Personal air monitoring during normal degreaser operations showed 5.5-h time-weighted average levels of HCFC-123 that ranged from 5.3 to 12.0 ppm (33.1 to 75.0 mg/m^3) throughout the facility, whereas short-term breathing-zone levels ranging from 160 to 460 ppm (1000 to 2880 mg/m^3) were measured in workers charging and unloading the degreaser. There was also one case of elevated liver enzymes with negative tests for viral hepatitis in a technician employed in the manufacturer's research laboratory where the degreaser was tested and evaluated. Static air levels in the laboratory were reported to be generally below 50 ppm (313 mg/m^3) HCFC-123.

In a factory in Japan where miniature heat exchangers were filled with HCFC-123 in a poorly ventilated room, 9 out of 14 workers were found to have elevated levels of liver enzymes 4–5 weeks after production had commenced (Takebayashi et al., 1998a,b).[1] Four of them were clinically ill, and two had jaundice. In these workers, AST and ALT were up to 20–30 times above the upper limit of the normal range. After an exhaust system was installed that maintains the concentration of airborne HCFC-123 at about 1 ppm (6.25 mg/m^3), trifluoroacetic acid was not detected in the workers' urine; at follow-up 1 year later, there were no further cases of clinical illness or elevated liver enzymes.[1] Exposure levels were not measured, but a simulation of the original working conditions indicated static air levels ranging from 5 to 1125 ppm (31.3 to 7030 mg/m^3) (6-h time-weighted average), depending on the distance from the filling area.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The available ecotoxicological data for HCFC-123 are summarized in Table 4. The data indicate that the chemical is, at most, slightly toxic to aquatic organisms under conditions of acute exposure. Chronic effects would not be expected because of limited aquatic persistence.

Trifluoroacetic acid, which is formed by atmospheric breakdown of HCFC-123, has been found to be of low toxicity in stream mesocosms, algae, higher plants, fish, and mammals (Boutonnet et al., 1999). The lowest threshold for any effect was 0.12 mg sodium trifluoroacetate/litre, above which the chemical had reversible effects on the growth of the alga *Selenastrum capricornutum.* In the most sensitive terrestrial species tested (sunflower), sodium trifluoroacetate at 1 mg/kg dry soil had clear effects on vegetative growth, whereas long-

[1] Also T. Takebayashi, personal communication, 1999 [cited in NICNAS, 1999].

term root exposure of wheat and soya to sodium trifluoroacetate at 1 mg/litre had no effect.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

There was inadequate information on the human health effects of short-term exposure to HCFC-123. In laboratory animals, HCFC-123 exhibits low acute toxicity, with an approximate oral lethal dose of 9 g/kg body weight, a 4-h LC_{50} by inhalation in the range of 28 400–52 600 ppm (178–329 g/m^3), and a dermal LD_{50} in excess of 2000 mg/kg body weight. It is not a skin irritant or sensitizer, but liquid HCFC-123 produces mild to moderate eye irritation. The critical effects associated with acute exposure are non-fatal liver damage, CNS depression, and cardiac sensitization to adrenaline. When inhaled in lethal concentrations, death was caused by severe CNS depression. For a single, 4-h exposure by inhalation, the LOAEL was 1000 ppm (6.25 g/m^3) for liver damage, based on liver cell necrosis and increased levels of circulating liver enzymes in guinea-pigs, and 5000 ppm (31.3 g/m^3) for CNS depression, based on failures in unconditioned reflexes in rats. The NOAEL for cardiac sensitization to adrenaline in dogs was 10 000 ppm (62.5 g/m^3). Although the dog is a very sensitive species, cardiac sensitization to adrenaline-induced arrhythmia is likely to be a relevant critical effect resulting from short-term exposure in humans, such as the sudden discharge of fire extinguishants in occupied rooms (NAS, 1996). Under these circumstances, CNS depression may also be a critical effect. A large number of short-chain halogenated hydrocarbons with different metabolic patterns have similar CNS and cardiac effects, which likely result from a direct anaesthetic action on neurons and myocardial cells (IPCS, 1990, 1991, 1992).

The critical effects associated with repeated exposure to HCFC-123 vapours are liver damage in humans as well as experimental animals, in addition to neonatal growth retardation, an increased incidence of benign tumours, and CNS depression, which have been recorded only in animals.

Based on a limited number of case reports, biochemical abnormalities associated with liver injury have been observed in humans at exposure levels in the order of 5–1125 ppm (31.3–7030 mg/m^3). The available data are insufficient to define the dose–response relationship in humans. Liver damage was also seen in rats, guinea-pigs, dogs, and monkeys. The lesions generally involved increased liver weight accompanied by hepatocyte enlargement and vacuolation at the lowest exposure levels, with necrosis, fatty change, and mild subacute inflammation at higher concentrations. They were associated with or preceded by increased levels of circulating liver enzymes and decreased serum triglycerides, glucose, and cholesterol. The LOAEL for liver effects in animals recorded in a well-conducted two-generation reproductive toxicity study in rats equalled 30 ppm (188 mg/m^3).

The cytotoxicity of HCFC-123 is probably due to the reactive metabolite trifluoroacetyl chloride, which can bind covalently to proteins and interfere with their function and/or alter their antigenicity. The 200 : 20 : 1 ratio of trifluoroacetylation of liver, kidney, and heart tissue proteins reported by Huwyler et al. (1992) and Huwyler & Gut (1992) correlates well with the observed effect levels for these organs in subchronic toxicity studies (Table 1) and probably reflects tissue differences in metabolic capacity.

There is no evidence that HCFC-123 is teratogenic in laboratory animals or induces reproductive or fetal toxicity at levels of exposure lower than those that cause other systemic effects in adults. Growth was retarded in neonatal rats and monkeys reared by dams exposed by inhalation to HCFC-123, with a LOAEL of 30 ppm (188 mg/m^3). The main metabolite of HCFC-123, trifluoroacetic acid, was found in the milk of the dams. As such, breastfed babies may represent a subpopulation that is uniquely sensitive to HCFC-123.

Reversible CNS depression was seen consistently in repeated-dose inhalation studies, but did not change in severity or duration with the number of exposures and was not associated with morphological changes in nervous tissues. As such, the mechanism of action is probably the same for both acute and chronic CNS depression. The lowest NOAEL for CNS effects from repeated administration was recorded in a neurotoxicity study in rats and equalled 300 ppm (1880 mg/m^3), based on a reduction in arousal.

Although there was evidence of clastogenic activity in human lymphocytes *in vitro* at high, cytotoxic concentrations, all other *in vitro* and *in vivo* tests for genetic toxicity were negative. Therefore, the evidence suggests that HCFC-123 is unlikely to be genotoxic *in vivo.*

In a 2-year inhalation study in rats, there was no exposure-related effect on the incidence of malignant tumours, but there was an increased incidence of hepatocellular adenomas, cholangiofibromas, pancreatic acinar cell adenomas, and Leydig adenomas. There was also an increase in the pre-cancerous lesions of hepatic foci of alteration, cholangiofibrosis, focal pancreatic acinar cell hyperplasia, and Leydig cell hyperplasia (Table 2). As stated above, HCFC-123 is unlikely to be

genotoxic *in vivo.* The minor, non-mutagenic metabolite 2-chloro-1,1,1-trifluoroethane caused an increased incidence of uterine carcinomas and Leydig cell adenomas in rats when given by oral gavage at 300 mg/kg body weight for 52 weeks (IPCS, 1992). However, only trace quantities would be formed from the metabolism of HCFC-123. Therefore, it is necessary to examine the mechanisms of tumour formation to establish if the modes of induction can be ruled out as relevant for humans:

- *Hepatocellular adenomas*. Several repeated-exposure studies have shown that HCFC-123 and its main metabolite, trifluoroacetic acid, like several other structurally diverse chemicals, induce peroxisome proliferation in rat hepatocytes (Warheit, 1993; Rusch et al., 1994; Malley et al., 1995; Keller et al., 1998). Peroxisome proliferators are generally not genotoxic but induce hepatocellular proliferation in rats and mice through a mechanism that appears to involve the expression of growth factors by hepatic macrophages, thus leading to liver tumour formation (Chevalier & Roberts, 1998). The hepatocellular adenomas seen in rats exposed to HCFC-123 may be related to the induction of peroxisome proliferation, which is a mechanism of questionable relevance for humans (Ashby et al., 1994). However, since the chemical is also hepatotoxic, which may have a role in the tumour formation, it is not possible to discount the hepatocellular adenomas as being of no concern to humans. It is, however, reasonable to adopt a threshold approach, based on adverse effects on the liver in subchronic exposure studies.

- *Cholangiofibromas.* Cholangiofibromas in the rat are atypical glandular structures lined by intestinal-like epithelium surrounded by dense connective tissue. Limited evidence from animal studies of various non-genotoxic chemicals, including chloroform and furan, suggests that this tumour type is associated with significant hepatocyte necrosis and regenerative cell proliferation that are relevant only at high dose/exposure levels (Elmore & Sirica, 1993; Jamison et al., 1996). In the 2-year rat study, cholangiofibromas and cholangiofibrosis occurred only in females exposed to HCFC-123 at 5000 ppm (31.3 g/m^3). The incidence of basophilic and eosinophilic foci of hepatocellular proliferation was also higher in females than in males (Table 2). Although the threshold level for the induction of cholangiofibromas in female rats was high, there is no mechanistic evidence that this tumour type can be dismissed with regard to its relevance to humans.

- *Pancreatic acinar cell adenomas*. Some hepatocarcinogenic peroxisome proliferators have been reported to induce tumours in other organs, including pancreatic acinar cell adenomas and Leydig cell adenomas, although these extrahepatic tumours appear not to be associated with peroxisome proliferation in the target organ (IARC, 1995). Although pancreatic acinar cell adenomas were found only in males at 1000 and 5000 ppm (6.25 and 31.3 g/m^3), the incidence was dose-related. Moreover, pancreatic acinar cell hyperplasia occurred in both sexes, likewise in a dose-dependent manner (Table 2). As such, until more is known about the mechanism for acinar cell tumour induction in animals and humans, the possibility that the pancreatic adenomas found in rats exposed to HCFC-123 may have some relevance to humans cannot be discounted.

- *Leydig cell adenomas*. The available studies indicate that exposure to HCFC-123 may be associated with endocrine disturbances in male rats, particularly in relation to prolactin release and serum LH concentrations. In rats, but not in humans, a decrease in serum prolactin causes a decrease in the number of LH receptors on Leydig cells and thus a decrease in testosterone production, which results in increased LH levels that in turn may induce Leydig cell hyperplasia and adenomas (Clegg et al., 1997). As such, it is conceivable that intermittent exposure to HCFC-123 could lead to fluctuations in prolactin and testosterone that in rats could induce transient increases in LH and, with time, Leydig cell growth and tumours. Although prolactin fluctuations would not be of concern in men, the effects of HCFC-123 on the sex hormone system are complex. Thus, in the absence of data from studies in primates, the increased incidence of Leydig cell adenomas in the 2-year rat study cannot be dismissed with respect to its relevance for humans.

In summary, it is likely that the benign tumours in the 2-year rat bioassay involve one or more non-genotoxic mechanisms, including peroxisome proliferation, hepatocellular damage, necrosis and regenerative proliferation, and disturbance of the hypothalamic-pituitary-testicular axis. Although humans may be less sensitive to tumours arising from some of these actions, overall it is not possible to discount the tumours in an evaluation of the potential risk for humans. Therefore, the increased incidence of benign tumours in the rat raises some concern with respect to the potential carcinogenicity in humans. The tumours probably arise from non-genotoxic mechanisms. In the 2-year bioassay, the tumour incidence was increased at 300 ppm (1.88 g/m^3), the lowest level tested, and a NOAEL was not established. In subchronic toxicity studies, the LOAEL based on any

adverse effect on the liver was 30 ppm (0.188 g/m^3) (Hughes, 1994; Malinverno et al., 1996).

11.1.2 Criteria for setting tolerable intakes or guidance values for HCFC-123

Derivation of a guidance value for HCFC-123 was outside the scope of the source documents (NICNAS, 1996, 1999). General advice about the derivation of tolerable intakes and guidance values for health-based exposure limits is set out in Environmental Health Criteria 170 (IPCS, 1994).

Exposure of the general public to HCFC-123 is likely to be minimal. The main risk to human health is through repeated occupational exposure via inhalation.

The critical effects of repeated low-level exposure to HCFC-123 are liver damage, which has been observed in all species investigated, including monkeys and humans, and retarded neonatal growth during lactation, which has been observed in rats and monkeys. In the absence of sufficient data to establish a dose–response relationship in humans, a guidance value for exposure to HCFC-123 must be based on the observed effect levels for liver lesions and retarded neonatal growth during lactation in pivotal animal studies. For both of these critical effects, a LOAEL of 30 ppm (188 mg/m^3) was established in a well-conducted two-generation reproductive toxicity study in rats, whereas a NOAEL was not achieved (Hughes, 1994; Malinverno et al., 1996).

The uncertainty factor applied to extrapolate from the LOAEL to a NOAEL must allow for the fact that whereas the recorded liver effects at the LOAEL were mild, hepatotoxicity may have a role in the induction of benign liver tumours in rats. Moreover, the growth retardation in neonates during lactation was in the order of 10–20%. It is likely that the liver effects are related to the formation of protein adducts with trifluoroacetyl chloride and that growth retardation in neonates is related to exposure to trifluoroacetic acid in maternal milk. Therefore, the uncertainty factor used to extrapolate the NOAEL from rats to humans must allow for the lack of *in vivo* data on the metabolic rate and other toxicokinetic properties of HCFC-123 in humans. Finally, an additional uncertainty factor must be applied to allow for human variability in toxicokinetics, as the metabolism of HCFC-123 to trifluoroacetyl chloride and trifluoroacetic acid is catalysed by CYP2E1 (Urban et al., 1994), whose activity is known to be influenced by genetic polymorphism, body weight, and dietary factors (Le Marchand et al., 1999).

11.1.3 Sample risk characterization

Adverse effects of HCFC-123 in animals and humans have been observed only at concentrations that were several orders of magnitude higher than those in the only known medium of exposure (air) in the general environment. The likelihood of public exposure as a consequence of catastrophic accidents or fire extinguishant discharges is very small, and the scale and duration of such exposures are expected to be low.

With respect to repeated occupational exposures, 3- to 8-h time-weighted average personal exposure levels in an HCFC-123 manufacturing plant were reported to be below 10 ppm (62.5 mg/m^3). Reported 2- to 12-h time-weighted average breathing-zone levels in machinery rooms containing air-conditioning equipment generally ranged from below 1 to 5 ppm (below 6.25 to 31.3 mg/m^3), whereas the use of a liquid HCFC-123 degreaser was associated with concentrations in the range of 5.3–12 ppm (33.1–75.0 mg/m^3) HCFC-123. The available case reports indicate that humans may develop biochemical signs of liver disease, such as elevated AST and ALT, after 1–4 months of repeated exposure to HCFC-123 at levels above 5 ppm (31.3 mg/m^3). Because the effects of low levels of HCFC-123 are due to toxic metabolites formed through CYP2E1, genetic, lifestyle, and dietary factors are expected to cause considerable variability in human susceptibility to the chemical.

11.2 Evaluation of environmental effects

Because of its high volatility, HCFC-123 released to the environment will partition almost entirely to the atmosphere. It is removed predominantly in the troposphere by reaction with hydroxyl radicals to form trifluoroacetic acid, and only a small fraction is transported to the stratosphere, where it may undergo photolysis and release chlorine radicals that catalyse the destruction of ozone. Because of its short atmospheric lifetime, estimated at 1.4 years, its ozone-depleting potential is low (0.02 relative to CFC-11). The global warming potential of HCFC-123 relative to carbon dioxide is 300, 93, and 29 over a time horizon of 20, 100, and 500 years, respectively (WMO, 1995).

The aquatic EC_{50}/LC_{50} values were below 100 mg/litre but above 10 mg/litre. As such, the chemical meets the European Community criteria for classification as harmful to the environment (Berends et al., 1999) and the globally harmonized criteria for classification as hazardous to the aquatic environment (Class: Acute III) (OECD, 1998). However, while HCFC-123 may be released to surface waters or soil, it is unlikely to persist in these media because of its high volatility. As such, it is

considered that HCFC-123 does not constitute a long-term or delayed danger to the aquatic environment.

Trifluoroacetic acid formed by degradation of HCFC-123 will precipitate in rain and may accumulate in closed aquatic systems such as salt lakes and seasonal wetlands. The maximum total contemporary deposition rate of trifluoroacetic acid from fluorocarbons has been estimated at 2800 tonnes a year, with 27% derived from HCFC-123 and the remainder from HCFC-124, HFC-134a, HFC-227ea, and the anaesthetic gases halothane and isoflurane (Boutonnet et al., 1999). In 2020, the maximum deposition from fluorocarbons is predicted to reach 160 000 tonnes a year, yielding a maximum average concentration of trifluoroacetic acid in rainwater of 0.1 µg/litre, which is several orders of magnitude lower than the no-effect level in both surface and soil water. By that year, HCFC-123 emissions will have declined, as the chemical will have been phased out in accordance with the Montreal Protocol. As such, it can be concluded that environmental levels of trifluoroacetic acid resulting from the breakdown of HCFC-123 do not pose a threat to the environment.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

A previous evaluation of HCFC-123 has been carried out by the International Programme on Chemical Safety (IPCS, 1992).

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document (Appendix 4).

REFERENCES

AIHA (1998) *Workplace environmental exposure level guide series: 1,1,1-Trifluoro-2,2-dichloroethane*. Fairfax, VA, American Industrial Hygiene Association Press.

Ashby J, Brady A, Elcombe CR, Elliott BM, Ishmael J, Odum J, Tugwood JD, Kettle S, Purchase IF (1994) Mechanistically-based human hazard assessment of peroxisome proliferator-induced hepatocarcinogenesis. *Human and experimental toxicology*, 13 (Suppl. 2):S1–S117.

Berends AG, de Rooij CG, Shin-ya S, Thompson RS (1999) Biodegradation and ecotoxicity of HFCs and HCFCs. *Archives of environmental contamination and toxicology*, 36(2):146–151.

Boutonnet JC, Bingham P, Calamari D, de Rooij C, Franklin J, Kawano T, Libre JM, McCulloch A, Malinverno G, Odom JM, Rusch GM, Smythe K, Sobolev I, Thompson R, Tiedje JM (1999) Environmental risk assessment of trifluoroacetic acid. *Human and ecological risk assessment*, 5(1):59–124.

Brewer WE, Smith S (1977) *Teratogenic study via inhalation with Genetron 123 in albino rats.* Morristown, NJ, Allied Chemical Corporation.

Britelli MR (1975) *Eye irritation test in rabbits.* Newark, DE, Du Pont de Nemours and Co.

Brock WJ (1988a) *Acute dermal toxicity study of HCFC-123 in rabbits.* Newark, DE, Du Pont de Nemours and Co.

Brock WJ (1988b) *Acute dermal toxicity study of HCFC-123 in rats.* Newark, DE, Du Pont de Nemours and Co.

Brock WJ (1988c) *Primary dermal irritation study with HCFC-123 in rabbits.* Newark, DE, Du Pont de Nemours and Co.

Buschman J (1996) *Crossover study with HCFC 123 in lactating Sprague-Dawley rats including additional studies on milk production and metabolites in offspring urine.* Hannover, Fraunhofer Institute for Toxicology and Aerosol Research.

Callander RD (1989) *HCFC-123 — an evaluation using the* Salmonella *mutagenicity assay.* Macclesfield, Cheshire, Imperial Chemical Industries Ltd.

Chang W-K, Criddle CS (1995) Biotransformation of HCFC-22, HCFC-142b, HCFC-123 and HFC-134a by methanotrophic mixed culture MM1. *Biodegradation*, 6(1):1–9.

Chevalier S, Roberts RA (1998) Perturbation of rodent hepatocyte growth control by nongenotoxic hepatocarcinogens — mechanisms and lack of relevance for human health. *Oncology reports*, 5:1319–1327.

Clayton JW (1966) *Acute inhalation toxicity.* Newark, DE, Du Pont de Nemours and Co.

Clegg ED, Cook JC, Chapin RE, Foster PMD, Daston GR (1997) Leydig cell hyperplasia and adenoma formation: Mechanisms and relevance to humans. *Reproductive toxicology,* 11:107–121.

Coate WB (1976) *LC_{50} of G123 in rats*. Vienna, VI, Hazleton Laboratories America Inc.

Cohen SD, Pumford NR, Khairallah EA, Boekelheide K, Pohl LR, Amouzadeh HR, Hinson JA (1997) Selective protein covalent binding and target organ toxicity. *Toxicology and applied pharmacology*, 143:1–12.

Coombs DW (1994) *HCFC-123 — 13-week inhalation neurotoxicity study in the rat.* Cambridgeshire, Huntingdon Research Centre Ltd.

Culik R, Kelly DP (1976) *Embryotoxic and teratogenic studies in rats with inhaled dichlorofluoromethane (Freon 21) and 2,2-dichloro-1,1,1-trifluoroethane (FC-123).* Newark, DE, Du Pont de Nemours and Co.

Dance CA (1991) In vitro *assessment of the clastogenic activity of HCFC-123 in cultured human lymphocytes.* Eye, Suffolk, Life Science Research Ltd. (No. 91/PFE003/0093).

Darr RW (1981) *An acute inhalation toxicity study of Fluorocarbon 123 in the Chinese hamster.* Morristown, NJ, Allied Corporation.

Dekant W (1993) *Metabolism of 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123)*. Würzburg, Institute of Toxicology, University of Würzburg (Report No. MA-250B-82-207).

Dodd DE, Brashear WT, Vinegar A (1993) Metabolism and pharmaco-kinetics of selected halon replacement candidates. *Toxicology letters*, 68:37–47.

Doleba-Crowe C (1978) *90-day inhalation exposure of rats and dogs to vapours of 2,2-dichloro-1,1,1-trifluoroethane (FC-123) (summary).* Newark, DE, Du Pont de Nemours and Co. [cited in NICNAS, 1996].

Du Pont (1993) *Workplace guidelines for Suva® Centri-LP (HCFC-123) in refrigeration and air conditioning applications.* Wilmington, DE, Du Pont de Nemours and Co.

Edwards CN (1991) *HCFC-123 (vapour phase):* In vitro *assessment of the clastogenic activity in cultured human lymphocytes.* Eye, Suffolk, Life Science Research Ltd. (No. 91/PFE002/0125).

Elmore LW, Sirica AE (1993) "Intestinal-type" of adenocarcinoma preferentially induced in right/caudate liver lobes of rats treated with furan. *Cancer research*, 53:254–259.

Frank H, Klein A, Renschen D (1996) Environmental trifluoroacetate. *Nature*, 382:34.

Fraser P (1994) *CSIRO report to SPA-AFEAS.* Canberra, Commonwealth Scientific and Industrial Research Organisation.

Goodman NC (1975) *Primary skin irritation and sensitization tests on guinea pigs.* Newark, DE, Du Pont de Nemours and Co.

Hall GT, Moore BL (1975) *Acute inhalation toxicity on Freon 123.* Newark, DE, Du Pont de Nemours and Co.

Harris JW, Jones JP, Martin JL, LaRosa AC, Olson MJ, Pohl LR, Anders MW (1992) Pentahaloethane-based chlorofluorocarbon substitutes and halothane: correlation of *in vivo* hepatic protein trifluoroacetylation and urinary trifluoroacetic acid excretion with calculated enthalpies of activation. *Chemical research in toxicology*, 5:720–725.

Hayman GD, Jenkin ME, Murrells TP, Johnson CE (1994) Tropospheric degradation chemistry of HCFC-123 (CF_3CHCl_2): a proposed replacement chlorofluorocarbon. *Atmospheric environment*, 28:421–437.

Henry JE (1975) *Acute oral test on FC-123.* Newark, DE, Du Pont de Nemours and Co. [cited in NICNAS, 1996].

Hoet P, Graf MLM, Bourdi M, Pohl LR, Duray PH, Chen W, Peter RM, Nelson SD, Verlinden N, Lison D (1997) Epidemic of liver disease caused by hydrochlorofluorocarbons used as ozone-sparing substitutes of chlorofluorocarbons. *Lancet*, 350:556–559.

Hofmann T (1995) *HCFC 123, HCFC 141B and HCF 134a, testing for subacute (2 weeks) inhalation toxicity in male and female Sprague Dawley rats.* Frankfurt am Main, Hoechst Aktiengesellschaft.

Hughes EW (1994) *HCFC 123: A study of the effect on reproductive function of two generations in the rat.* Huntingdon, Cambridgeshire, Huntingdon Research Centre Ltd.

Huwyler J, Gut J (1992) Exposure to the chlorofluorocarbon substitute 2,2-dichloro-1,1,1-trifluoroethane and the anaesthetic agent halothane is associated with transient adduct formation in the heart. *Biochemical and biophysical research communications*, 184:1344–1349.

Huwyler J, Aeschlimann D, Christen U, Gut J (1992) The kidney as a novel target tissue for protein adduct formation associated with metabolism of halothane and the candidate chlorofluorocarbon replacement 2,2-dichloro-1,1,1-trifluoroethane. *European journal of biochemistry*, 207:229–238.

IARC (1995) Peroxisome proliferation and its role in carcinogenesis: views and expert opinions of an IARC working group, Lyon, 7–11 December 1994. Lyon, International Agency for Research on Cancer.

ICI (1992) *An evaluation in the* in vitro *cytogenetic assay using human lymphocytes.* Macclesfield, Cheshire, Imperial Chemical Industries Ltd. [cited in AIHA, 1998].

Industrial Bio-Test Laboratories (1977) *90-day subacute inhalation toxicity study with Genetron 123 in albino rats.* Northbrook, IL, Industrial Bio-Test Laboratories, Inc.

IPCS (1990) *Fully halogenated chlorofluorocarbons.* Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 113).

IPCS (1991) *Partially halogenated chlorofluorocarbons (methane derivatives)*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 126).

IPCS (1992) *Partially halogenated chlorofluorocarbons (ethane derivatives)*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 139).

IPCS (1998) *International Chemical Safety Card — 2,2-Dichloro-1,1,1-trifluoroethane.* Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 1343).

IPCS (1994) *Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 170).

Jamison KC, Larson JL, Butterworth BE, Harden R, Skinner BL, Wolf DC (1996) A non-bile duct origin for intestinal crypt-like ducts with peritubular fibrosis induced in livers of F344 rats by chloroform inhalation. *Carcinogenesis*, 17:675–682.

Jenkins CA (1992a) *HCFC-123 (liquid): Biotic degradation closed bottle test.* Eye, Suffolk, Life Sciences Research Ltd. (No. 91/PFE008/0477).

Jenkins CA (1992b) *HCFC-123: Acute toxicity to rainbow trout.* Eye, Suffolk, Life Sciences Research Ltd. (No. 91/PFE004/0939).

Jenkins CA (1992c) *HCFC-123: Acute toxicity to* Daphnia magna. Eye, Suffolk, Life Sciences Research Ltd. (No. 91/PFE006/0972).

Jenkins CA (1992d) *HCFC-123: Determination of its* EC_{50} *to* Selenastrum capricornutum. Eye, Suffolk, Life Sciences Research Ltd (No. 91/PFE007/0935).

Keller DA, Lieder PH, Brock WJ, Cook JC (1998) 1,1,1-Trifluoro-2,2-dichloroethane (HCFC-123) and 1,1,1-trifluoro-2-bromo-2-chloroethane (halothane) cause similar biochemical effects in rats exposed by inhalation for five days. *Drug and chemical toxicology*, 21:405–415.

Kelly DP (1989) *Four-week inhalation toxicity study with HCFC-123 in rats.* Newark, DE, Du Pont de Nemours and Co.

Kennelly JC (1993) *HCFC 123: Assessment for the introduction of unscheduled DNA synthesis in rat liver after inhalation exposure.* Macclesfield, Cheshire, Zeneca Ltd.

Kotamarthi VR, Rodriguez JM, Ko MKW, Tromp TK, Sze ND, Prather MJ (1998) Trifluoroacetic acid from degradation of HCFCs and HFCs — a three-dimensional modelling study. *Journal of geophysical research*, 103:5747–5758.

Le Marchand L, Wilkinson GR, Wilkens LR (1999) Genetic and dietary predictors of CYP2E1 activity: a phenotyping study in Hawaii Japanese using chlorzoxazone. *Cancer epidemiology, biomarkers and prevention*, 8:495–500.

Lewis RW (1990) *28-day inhalation study to assess changes in rat liver and plasma.* Macclesfield, Cheshire, Imperial Chemical Industries Ltd.

Lind RC, Gandolfi AJ, Hall PM (1995) Biotransformation and hepato-toxicity of HCFC-123 in the guinea pig: Potentiation of hepatic injury by prior glutathione depletion. *Toxicology and applied pharmacology*, 134:175–181.

Loizou GD, Urban G, Dekant W, Anders MW (1994) Gas-uptake pharmacokinetics of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). *Drug metabolism and disposition*, 22:511–517.

Longstaff E, Robinson M, Bradbrook C, Styles JA, Purchase IF (1984) Genotoxicity and carcinogenicity of fluorocarbons: Assessment by short-term *in vitro* tests and chronic exposure in rats. *Toxicology and applied pharmacology*, 72:15–31.

Malinverno G, Rusch GM, Millischer RJ, Hughes EW, Schroeder RE, Coombs DW (1996) Inhalation teratology and reproduction studies with 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123). *Fundamental and applied toxicology*, 23:276–287.

Malley LA (1990) *Subchronic inhalation toxicity: 90-day study with HCFC-123 in rats.* Newark, DE, Du Pont de Nemours and Co.

Malley LA (1992) *Combined chronic toxicity/oncogenicity study with HCFC-123: Two-year inhalation toxicity study in rats.* Newark, DE, Du Pont de Nemours and Co.

Malley LA, Carakostas M, Hansen JF, Rusch GM, Kelly DP, Trochimowicz HJ (1995) Two-year inhalation toxicity study in rats with hydrochlorofluorocarbon 123. *Fundamental and applied toxicology*, 25:101–114.

Malley LA, Carakostas M, Elliott GS, Alvarez L, Schroeder RE, Frame SR, Van Pelt C, Trochimowicz HJ, Rusch GM (1996) Subchronic toxicity and teratogenicity of 2-chloro-1,1,1,2-tetrafluoroethane (HCFC-124). *Fundamental and applied toxicology*, 32:11–22.

Marit GB, Dodd DE, George ME, Vinegar A (1994) Hepatotoxicity in guinea pigs following acute exposure to 1,1-dichloro-2,2,2-trifluoro-ethane. *Toxicologic pathology*, 22(4):404–414.

Marshal RR (1992) *Evaluation of chromosome aberration frequencies in cultured peripheral blood lymphocytes from rats treated with HCFC-123.* Harrogate, Yorkshire, Hazleton Microtest.

MRI (1991) *Results of employee exposure monitoring for HCFC-123 at centrifugal chiller installations.* Final report submitted to the US Environmental Protection Agency. Silver Spring, MD, Meridian Research, Inc.

MRI (1993a) *Assessment of firefighter exposure to HCFC-123 during extinguishant efficiency tests conducted at the United States Naval Air Station in Beaufort, South Carolina.* Draft report submitted to the US

Environmental Protection Agency. Silver Spring, MD, Meridian Research, Inc.

MRI (1993b) *Assessment of firefighter exposure to HCFC-123 during fire extinguisher use in aircraft hangars.* Draft report submitted to American Pacific Corporation. Silver Spring, MD, Meridian Research, Inc.

Muller W, Hofmann T (1988) *HCFC-123 — micronucleus test in male and female NMRI mice after inhalation.* Frankfurt am Main, Hoechst Aktiengesellschaft.

Mullin LS (1976) *Behavioural toxicity testing of Fluorocarbon 123 in rats.* Newark, DE, Du Pont de Nemours and Co.

NAS (1996) *Toxicity of alternatives to chlorofluorocarbons: HFC-134a and HCFC-123.* Washington, DC, National Academy of Sciences, National Academy Press.

NICNAS (1996) *Priority Existing Chemical No. 4 — 2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123), full public report, National Industrial Chemicals Notification and Assessment Scheme.* Canberra, Australian Government Publishing Service.

NICNAS (1999) *2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123): Secondary Notification No. 4S, full public report. National Industrial Chemicals Notification and Assessment Scheme.* Sydney, National Occupational Health and Safety Commission.

OECD (1998) *Agreed harmonized integrated hazard classification system for human health and environmental effects of chemical substances.* Paris, Organisation for Economic Co-operation and Development, Environmental Health and Safety Division.

Oremland RS, Lonergan DJ, Culbertson CW, Lovley DR (1996) Microbial degradation of hydrofluorocarbons ($CHCl_2F$ and $CHCl_2CF_3$) in soils and sediments. *Applied and environmental microbiology*, 62(5):1818–1821.

Pierson K (1990a) *Flow-through acute 96 hour LC_{50} of HCFC-123 in fathead minnows (*Pimephales promelas*)*. Newark, DE, Du Pont de Nemours and Co.

Pierson K (1990b) *Static acute 48 hour LC_{50} of HCFC-123 in* Daphnia magna*.* Newark, DE, Du Pont de Nemours and Co.

Rusch GM, Trochimowitz HJ, Malley LJ, Kelly DP, Peckham J, Hansen J, Charm JB (1994) Subchronic inhalation toxicity studies with hydrochlorofluorocarbon 123 (HCFC 123). *Fundamental and applied toxicology*, 23:169–178.

Sandow J, Jerabek-Sandow G, Fenner-Nau D (1995a) *Effect of fluorocarbons on pituitary-gonadal function in a 14-day inhalation toxicity study: HCFC 123 (Frigen), HCFC 141b (difluorchlorethane) and HFC 134a (tetrafluorethane).* Frankfurt am Main, Hoechst Aktiengesellschaft.

Sandow J, Rechenberg W, Jerabek-Sandow G (1995b) *Effect of HCFC-123 on androgen biosynthesis and gonadotropin secretion in rats.* Frankfurt am Main, Hoechst Aktiengesellschaft.

Sibley H (1992) *A study for determining refrigerant exposure levels while servicing an HCFC-123 centrifugal chiller.* Syracuse, NY, Carrier Corporation.

Slauter RW (1997) *HCFC 123: Inhalation study in pregnant monkeys to assess milk transfer and composition following postpartum exposure.* Mattawan, MI, MPI Research.

Takebayashi T, Kabe I, Endo Y, Tanaka S, Miyauchi H, Nozi K, Takahashi K, Omae K (1998a) Acute liver dysfunction among workers exposed to 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123): A case report. *Journal of occupational health*, 40:169–170.

Takebayashi T, Kabe I, Endo Y, Tanaka S, Miyauchi H, Nozi K, Imamiya S, Takahashi K, Omae K (1998b) Exposure to 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123): A causal inference. *Journal of occupational health*, 40:334–338.

Tanaka S, Kabe I, Takebayashi T, Endo Y, Miyauchi H, Nozi K, Takahashi K, Seki Y, Omae K (1998) Environmental and biological monitoring of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). *Journal of occupational health*, 40:348–349.

Trane Company (1991) *Report on testing and analysis of the concentration of HCFC-123 in field installations with general machinery rooms containing hermetic centrifugal chillers.* La Crosse, WI, The Trane Company.

Trane Company (1992) *Report of worker exposure to HCFC-123 during servicing of hermetic centrifugal chillers.* La Crosse, WI, The Trane Company.

Trochimowicz HJ, Mullin LS (1973) *Cardiac sensitization potential (EC_{50}) of trifluoro-dichloroethane.* Newark, DE, Du Pont de Nemours and Co.

UNEP (1999) Ozone treaties. <http://www.unep.org/ozone/treaties.htm>. United Nations Environment Programme.

Urban G, Dekant W (1994) Metabolism of 1,1-dichloro-2,2,2-trifluoroethane in rats. *Xenobiotica*, 24:881–892.

Urban G, Speerschneider P, Dekant W (1994) Metabolism of the chlorofluorocarbon substitute 1,1-dichloro-2,2,2-trifluoroethane by rat and human liver microsomes: the role of cytochrome P450 2E1. *Chemical research in toxicology*, 7:170–176.

Vinegar A, Williams RJ, Fisher JW, McDougal JN (1994) Dose-dependent metabolism of 2,2-dichloro-1,1,1-trifluoroethane: A physiologically based pharmacokinetic model in the male Fischer 344 rat. *Toxicology and applied pharmacology*, 129:103–113.

Wang Y, Olson MJ, Baker MT (1993) Interaction of fluoroethane chlorofluorocarbon (CFC) substitutes with microsomal cytochrome P450. *Biochemical pharmacology*, 46:87–94.

Warheit DB (1993) *Mechanistic studies with HCFC-123.* Newark, DE, Du Pont de Nemours and Co.

Williams RJ, Vinegar A, McDougal JN, Jarabek AM, Fisher JW (1996) Rat to human extrapolation of HCFC-123 kinetics deduced from halothane kinetics — a corollary approach to physiologically based pharmacokinetic modeling. *Fundamental and applied toxicology*, 30:55–66.

WMO (1995) *Scientific assessment of ozone depletion*. Geneva, World Meteorological Organization (Global Ozone Research and Monitoring Project Report No. 37).

Wujcik CE, Zehavi D, Seiber JN (1998) Trifluoroacetic acid levels in 1994–1996 fog, rain, snow and surface waters from California and Nevada. *Chemosphere*, 36:1233–1245.

APPENDIX 1 — SOURCE DOCUMENTS

NICNAS (1996): *Priority Existing Chemical No. 4 — 2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123), full public report, National Industrial Chemicals Notification and Assessment Scheme*

Copies of the NICNAS (1996) report on HCFC-123 (prepared by S. Batt, L. Onyon, L. Slosu, and D. Willcocks) may be obtained from:

NICNAS
Existing Chemicals
GPO Box 58
Sydney NSW 2001
Australia

NICNAS reports are prepared to meet the requirements of the *Industrial Chemicals Notification and Assessment Act, 1989*, as amended. In the preparation of the assessment report, both internal and external peer reviews are undertaken. Under the NICNAS legislation, applicants for the assessment of a chemical (i.e., importers and manufacturers of a chemical) may apply for variations to the draft report. The following companies and industry associations participated in the review of the assessment at this stage: Association of Fluorocarbon Consumers and Manufacturers, Elf Atochem (Australia) Pty Ltd, Lovelock Luke Pty Ltd, and North American Fire Guardian Technology (Australia) Pty Ltd. The report was also open for public comment.

NICNAS (1999): *2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123): Secondary Notification No. 4S, full public report. National Industrial Chemicals Notification and Assessment Scheme*

Copies of the NICNAS (1999) report on HCFC-123 (prepared by S. Batt, S. Kristensen, and C. Lee-Steere) may be obtained from:

NICNAS
Existing Chemicals
GPO Box 58
Sydney NSW 2001
Australia

NICNAS reports are prepared to meet the requirements of the *Industrial Chemicals Notification and Assessment Act, 1989*, as amended. In the preparation of the assessment report, both internal and external peer reviews are undertaken. Under the NICNAS legislation, applicants for the reassessment of a chemical (i.e., importers and manufacturers of a chemical) may apply for variations to the draft report. The following companies participated in the review of the assessment at this stage: Du Pont (Australia) Pty Ltd, Elf Atochem (Australia) Pty Ltd, GSA Industries (Australia) Pty Ltd, MSA (Australia) Pty Ltd, North American Fire Guardian Technology (Australia) Pty Ltd, and Solvents Australia Pty Ltd. The report was also open for public comment.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on HCFC-123 was sent for review to institutions and organizations identified by IPCS after contact with IPCS National Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

Alexandria University, Faculty of Agriculture, Department of Pesticide Chemistry, Egypt

AlliedSignal, Department of Toxicology and Risk Assessment, Health, Safety, Environment and Remediation, USA

Department of Health, Protection of Health Division, United Kingdom

DuPont Fluoroproducts, Haskell Laboratory for Toxicology and Industrial Medicine, USA

Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany

Glaxo Wellcome Research and Development, Medicines Safety Evaluation Division, United Kingdom

Health and Safety Executive, United Kingdom

Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada

Institute of Terrestrial Ecology, United Kingdom

National Chemicals Inspectorate (KEMI), Sweden

National Institute for Occupational Safety and Health, USA

National Institute of Environmental Health Sciences, National Institutes of Health, USA

National Institute of Public Health, Centre of Industrial Hygiene and Occupational Diseases, Czech Republic

Université Catholique de Louvain, Faculté de Médecine, Belgique

US Environmental Protection Agency, Drinking Water Program, Region VIII, USA

World Health Organization, International Programme on Chemical Safety, Switzerland

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Sydney, Australia, 21–24 November 1999

Members

Dr R. Benson, Drinking Water Program, US Environmental Protection Agency, Region VIII, Denver, CO, USA

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden

Dr R.M. Bruce, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom

Dr R.S. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

Dr S. Chou, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood, Cambridgeshire, United Kingdom

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Aerosol Research, Hannover, Germany

Dr S. Kristensen, National Occupational Health and Safety Commission (Worksafe), Sydney, NSW, Australia

Mr C. Lee-Steere, Environment Australia, Canberra, ACT, Australia

Ms M. Meek, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Ms F. Rice, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr J. Sekizawa, National Institute of Health Sciences, Tokyo, Japan

Dr D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Sydney, NSW, Australia (*Chairperson*)

Professor P. Yao, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, People's Republic of China

Observers

Mr P. Howe, Institute of Terrestrial Ecology, Huntingdon, Cambridgeshire, United Kingdom

Dr K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit, GmbH, Oberschleissheim, Germany

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Ms M. Godden, Health and Safety Executive, Bootle, Merseyside, United Kingdom

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

2,2-DICHLORO-1,1,1-TRIFLUOROETHANE

1343
November 1998

CAS No: 306-83-2
RTECS No: KI1108000

HCFC 123
$C_2HCl_2F_3$ / $CHCl_2CF_3$
Molecular mass: 152.9

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible.	NO open flames.	In case of fire in the surroundings: all extinguishing agents allowed.
EXPLOSION			In case of fire: keep drums, etc., cool by spraying with water.
EXPOSURE			
Inhalation	Confusion. Dizziness. Drowsiness. Unconsciousness.	Local exhaust or breathing protection.	Fresh air, rest. Artificial respiration if indicated. Refer for medical attention.
Skin		Protective gloves.	Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	(See Inhalation).		Rest.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Collect leaking liquid in sealable containers. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT let this chemical enter the environment. Chemical protection suit including self-contained breathing apparatus.	

EMERGENCY RESPONSE	STORAGE
	Keep in a well-ventilated room.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
COLOURLESS LIQUID, WITH CHARACTERISTIC ODOUR.

Physical dangers
The vapour is heavier than air and may accumulate in low ceiling spaces causing deficiency of oxygen.

Chemical dangers
The substance decomposes on heating producing phosgene, hydrogen fluoride and hydrogen chloride.

Occupational exposure limits
TLV not established.

Routes of exposure
The substance can be absorbed into the body by inhalation.

Inhalation risk
No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

Effects of short-term exposure
The substance irritates the eyes. The substance may cause effects on the central nervous system and cardiovascular system, resulting in narcosis and cardiac disorders.

Effects of long-term or repeated exposure
The substance may have effects on the liver.

PHYSICAL PROPERTIES

Boiling point: 28°C
Melting point: -107°C
Relative density (water = 1): 1.5
Solubility in water, g/100 ml at 25°C: 0.21
Vapour pressure, Pa at 25°C: 14
Relative vapour density (air = 1): 6.4

ENVIRONMENTAL DATA

This substance may be hazardous to the environment; special attention should be given to its impact on the ozone layer. It is strongly advised not to let the chemical enter into the environment because it persists in the environment. Avoid release to the environment in circumstances different to normal use.

NOTES

High concentrations in the air cause a deficiency of oxygen with the risk of unconsciousness or death.
Check oxygen content before entering area.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD repose principalement sur un certain nombre d'évaluations relatives aux effets du 2,2-dichloro-1,1,1-trifluoréthane (HCFC-123), évaluations qui relèvent soit de la protection de l'environnement, soit de la médecine du travail. Ces travaux ont été effectués dans le cadre de l'Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) et publiés en mars 1996 (NICNAS, 1996) et en juillet 1999 (NICNAS, 1999). Les données intéressantes publiées depuis la parution des rapports du NICNAS ou obtenues par une recherche approfondie portant sur plusieurs bases de données jusqu'à août 1999 ont également fait l'objet d'une étude critique et incluses dans le présent CICAD. Ce document constitue une mise à jour de l'étude du HCFC-123 qui figure dans la monographie consacrée à ce type de composé (Critère d'Hygiène de l'Environnement No 139) (IPCS, 1992). Cette mise à jour à été suscitée par la publication de données nouvelles et importantes sur le composé. On trouvera à l'appendice 1 des indications sur la nature des examens par des pairs ainsi que sur les sources documentaires utilisées. L'appendice 2 donne des renseignements sur l'examen de ce CICAD par des pairs. La publication de ce CICAD a été approuvée lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Sydney (Australie) du 21 au 24 novembre 1999. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information internationale sur la sécurité chimique (ICSC 1343) relative au 2,2-dichloro-1,1,1-trifluoréthane, établie par le Programme international sur la sécurité chimique, est également reproduite dans l'appendice 4 (IPCS, 1998).

Le HCFC-123 (No CAS 306-83-2) est un composé de synthèse qui se présente sous la forme d'un liquide volatil incombustible. Il est utilisé comme réfrigérant dans les installations de climatisation commerciales et industrielles; il entre dans la composition de certain produits gazeux anti-feu et sert également d'agent d'expansion pour mousses. On l'emploie aussi pour le nettoyage des métaux et du matériel électronique. Son agressivité vis-à-vis de la couche d'ozone ne représente que le 2 % de celle du CFC-11 (trichlorofluorométhane). Par rapport au dioxyde de carbone, on estime que son potentiel de réchauffement du climat est de 300 sur une vingtaine d'années. C'est pourquoi on l'utilise provisoirement pour remplacer les chloro- et bromo-fluorocarbures auxquels il a été décidé de renoncer aux termes du Protocole de Montréal sur les substances qui détruisent la couche d'ozone. Selon l'Amendement de Copenhague au Protocole de Montréal, le HCFC-123 et les autres hydrocarbures fluorés devront être éliminés d'ici 2020.

Les émissions de HCFC-123 se font principalement dans l'air ambiant. Bien que légèrement toxique pour les poissons, les daphnies et les algues, ce composé ne devrait pas constituer de réel danger pour le milieu aquatique car il ne persiste pas dans l'eau, même à des concentrations inférieures à sa limite de solubilité. On estime que sa demi-vie dans l'atmosphère est inférieure à 2 ans. Comme pour d'autres fluorocarbures plus courants, son principal produit de décomposition dans l'atmosphère est l'acide trifluoracétique, qui se répartit dans les diverses phases aqueuses de l'environnement. L'acide trifluoracétique est difficilement dégradable et il est susceptible de s'accumuler dans certains systèmes aquatiques fermés, mais sa concentration actuelle ou prévisible compte tenu des émissions de HCFC-123 est inférieure au seuil de toxicité.

On pense que l'exposition de la population générale au HCFC-123 est minime. Il existe cependant une possibilité d'exposition professionnelle lors de la production du composé ou de la préparation et de l'utilisation de produits qui en contiennent.

On sait peu de chose concernant les effets du HCFC-123 sur l'organisme humain. On a fait état de cas d'étourdissements, de céphalées et de nausées à la suite d'une seule et unique exposition à une concentration inconnue de ce composé dans l'air ambiant. Par ailleurs, des cas d'atteinte hépatique manifeste ou infraclinique ont été également observés après exposition professionnelle pendant 1 à 4 mois à des vapeurs de HCFC-123 dont la concentration était comprise entre 5 et 1125 ppm (31,3-7030 mg/m^3).

Le HCFC-123 présente une faible toxicité aiguë pour les animaux de laboratoire. En le faisant inhaler pendant quelques minutes à plusieurs heures par divers animaux d'expérience on a constaté à la dose de 1000 ppm (6,25 g/m^3) des lésions au niveau du foie chez les cobayes, une dépression du système nerveux central (SNC) chez toutes les espèces à la dose de 5000 ppm (31,3 g/m^3) et une arythmie cardiaque induite par l'adrénaline à la dose de 20 000 ppm (125 g/m^3) chez des chiens. Chez le rat et le hamster, l'inhalation du composé à des doses supérieures à 30 000 ppm (188 g/m^3) pendant 4 heures provoque une grave dépression du SNC conduisant à la mort. Le HCFC-123 n'est pas irritant pour la peau et il ne produit pas de sensibilisation, mais il peut irriter la muqueuse oculaire lorsqu'il est à l'état liquide. Lors d'études toxicologiques de 2 à 39 semaines consistant à faire inhaler de manière répétée le produit par des animaux de laboratoire (rats, cobayes, chiens et

singes), on a constaté que les principaux organes cibles étaient le foie, le système endocrine hypothalamo-hypophyso-gonadique et le SNC. La concentration minimale produisant un effet nocif observable (LOAEL) avec comme critère les effets hépatiques a été trouvée égale à 30 ppm (188 mg/m^3). En prenant comme critère les effets sur le système endocrine, la concentration sans effet nocif observable (NOAEL) était égale à 100 ppm (625 mg/m^3) et dans le cas des effets sur le SNC, elle était égale à 300 ppm (1880 mg/m^3). Rien n'indique que le HCFC-123 ait des effets tératogènes chez les animaux de laboratoire, ni qu'il présente une toxicité génésique ou foetale à des doses inférieures à celles qui ont d'autres effets toxiques généraux. Des ratons et des singes nouveau-nés dont les mères allaitantes avaient été exposées à du HCFC-123 à une concentration égale à la LOAEL (30 ppm ou 188 mg/m^3), ont présenté un retard de croissance. Le métabolite principal (acide trifluor-acétique) a été retrouvé dans le lait des mères allaitantes.

Des signes d'activité clastogène ont été relevés dans des lymphocytes humains mis en présence de HCFC-123 *in vitro* à des doses suffisamment élevées pour être cytotoxiques, mais tous les autres tests de génotoxicité effectués *in vitro* ou *in vivo* se sont révélés négatifs. On voit donc que ce composé est vraisem-blablement dénué de génotoxicité *in vivo.*

Lors d'une étude de 2 ans au cours de laquelle on a fait inhaler le produit à des rats, on a constaté une augmentation de l'incidence des lésions précancéreuses et des tumeurs bénignes du foie, du pancréas et des testicules, mais aucun accroissement de l'incidence des tumeurs malignes qui soit attribuable à ce traitement. Il est probable que la formation de ces tumeurs implique un ou plusieurs mécanismes non génotoxiques, notamment une prolifération des peroxysomes, des lésions au niveau des hépatocytes, une nécrose et une prolifération dégénérative ainsi qu'une perturbation de l'axe hypothalamo-hypophyso-gonadique. Il est possible que l'organisme humain soit moins sensible à la formation de tumeurs par l'un ou l'autre de ces mécanismes, mais on ne peut cependant ne pas tenir compte de ces tumeurs dans une évaluation du risque pour l'Homme.

L'effet le plus significatif dans le cas d'une seule et unique exposition au HCFC-123, comme cela peut se produire lors de son utilisation pour éteindre un feu, consiste dans son action dépressive sur le système nerveux central à laquelle s'ajoute la possibilité d'un accroissement des arythmies cardiaques induites par l'adrénaline. En cas d'exposition répétée, l'effet le plus significatif est la possibilité de lésions hépatiques, effet qui a été observé chez des ouvriers exposés à des concentrations atmosphériques supérieures à 5 ppm (31,3 mg/m^3) pendant 1 à 4 mois.

RESUMEN DE ORIENTACIÓN

Este CICAD se basa principalmente en las evaluaciones de la salud ocupacional y los efectos en el medio ambiente del 2,2-dicloro-1,1,1-trifluoroetano (HCFC-123) realizadas en el marco del Plan Nacional Australiano de Notificación y Evaluación de Sustancias Químicas Industriales (NICNAS) y publicadas en marzo de 1996 (NICNAS, 1996) y julio de 1999 (NICNAS, 1999). También se ha evaluado e incorporado a este CICAD la información aparecida desde la terminación de los informes del NICNAS y la obtenida en una búsqueda amplia efectuada en varias bases de datos en línea hasta agosto de 1999. Este CICAD es una actualización del examen del HCFC-123 de la monografía Criterios de Salud Ambiental 139 (IPCS, 1992), necesaria tras la aparición de nuevos datos significativos. La información relativa al carácter del examen colegiado y a la disponibilidad de los documentos originales figura en el apéndice 1. La información sobre el examen colegiado de este CICAD se presenta en el apéndice 2. Su publicación se aprobó en una reunión de la Junta de Evaluación Final celebrada en Sydney, Australia, los días 21-24 de noviembre de 1999. En el apéndice 3 figura la lista de participantes en la Junta de Evaluación Final. La Ficha internacional de seguridad química (ICSC 1343) para el 2,2-dicloro-1,1,1-trifluoroetano, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1998), también se reproduce en el apéndice 4.

El HCFC-123 (CAS Nº 306-83-2) es un líquido sintético, no combustible, volátil, que se utiliza como refrigerante en instalaciones de aire acondicionado comerciales e industriales, en extintores de incendios gaseosos, como agente espumante y en la limpieza de metales y de componentes electrónicos. Su capacidad de agotamiento del ozono es solamente el 2% de la que tiene el CFC-11 (triclorofluorometano). Su potencial de calentamiento de la Tierra es de 300 en una perspectiva cronológica de 20 años con respecto al anhídrido carbónico. El HCFC-123 como tal se utiliza en la actualidad de manera transitoria para sustituir los clorofluorocarburos y los bromofluorocarburos, que son objeto de supresión progresiva en aplicación del Protocolo de Montreal relativo a las sustancias que agotan la capa de ozono. La Enmienda de Copenhague al Protocolo de Montreal de 1992 exige la eliminación progresiva del HCFC-123 y de otros hidroclorofluoro-carburos para el año 2020.

El HCFC-123 se libera en el medio ambiente fundamentalmente en el aire atmosférico. Si bien es ligeramente tóxico para los peces, *Daphnia* y las algas, no es probable que represente un peligro importante para el medio acuático, dada su escasa persistencia en el agua, incluso en concentraciones inferiores al límite de solubilidad. En la atmósfera, el HCFC-123 tiene una vida estimada de menos de dos años. El principal producto de degradación atmosférica del HCFC-123 (y de otros fluorocarburos más ampliamente utilizados) es el ácido trifluoroacético, que se distribuye en las fases acuosas del medio ambiente. Aunque este ácido es resistente a la degradación y puede acumularse en determinados sistemas acuáticos cerrados, las concentraciones actuales y previstas a partir de las emisiones de HCFC-123 son inferiores a los umbrales tóxicos.

Se prevé una exposición mínima del público general al HCFC-123. Sin embargo, es posible la exposición ocupacional durante la fabricación del HCFC-123 y la fabricación y el uso de productos que lo contienen.

Se dispone de una información limitada sobre los efectos del HCFC-123 en el ser humano. Se han notificado casos de vértigo, dolor de cabeza y náuseas tras una exposición aislada a concentraciones desconocidas de HCFC-123 en el aire, así como casos de enfermedad hepática manifiesta o subclínica asociada con exposiciones ocupacionales repetidas a vapores de HCFC-123 en concentraciones de 5-1125 ppm (31,3-7030 mg/m^3) durante 1-4 meses.

La toxicidad aguda del HCFC-123 en animales de laboratorio es baja. La inhalación durante un período comprendido entre unos minutos y unas horas provoca lesiones hepáticas en los cobayas con 1000 ppm (6,25 g/m^3), depresión del sistema nervioso central en todas las especies examinadas con 5000 ppm (31,3 g/m^3) y arritmia cardíaca inducida por la adrenalina en perros con 20 000 ppm (125 g/m^3). En la rata y el hámster, la inhalación de más de 30 000 ppm (188 g/m^3) durante cuatro horas provoca una fuerte depresión del sistema nervioso central y la muerte. El HCFC-123 no es irritante o sensibilizador cutáneo, pero en forma líquida puede causar irritación ocular. En estudios de toxicidad por inhalación con exposiciones repetidas durante un período de 2 a 39 semanas en ratas, cobayas, perros y monos, los órganos más afectados fueron el hígado, el sistema endocrino del hipotálamo, la hipófisis y las gónadas y el sistema nervioso central. La concentración más baja con efectos adversos observados (LOAEL) basada en los efectos hepáticos fue de 30 ppm (188 mg/m^3). La concentración sin efectos adversos observados (NOAEL) fue de 100 ppm (625 mg/m^3) basada en los efectos endocrinos y de 300 ppm (1880 mg/m^3) basada en los efectos en el sistema nervioso central. No hay pruebas de que el HCFC-123 sea teratogénico o induzca toxicidad reproductiva o fetal

con niveles de exposición inferiores a los que provocan otros efectos sistémicos. Se observó un crecimiento retardado en ratas y monos recién nacidos de madres expuestas al HCFC-123, con una LOAEL de 30 ppm (188 mg/m^3). En la leche de las madres se detectó ácido trifluoroacético, principal metabolito del HCFC-123.

Aunque se obtuvieron pruebas de actividad clastogénica en los linfocitos humanos expuestos a concentraciones altas citotóxicas de HCFC-123 *in vitro,* todas las demás pruebas de toxicidad genética *in vitro* e *in vivo* dieron resultados negativos. Por consiguiente, las pruebas parecen indicar que no es probable que este producto químico tenga actividad genotóxica *in vivo.*

En un estudio de inhalación de dos años en ratas se observó una mayor incidencia de lesiones precancerosas y tumores benignos en el hígado, el páncreas y los testículos, pero no se detectó un aumento de la incidencia de tumores malignos relacionado con la exposición. Probablemente se debe a que en estos tumores intervienen uno o más mecanismos no genotóxicos por ejemplo, la proliferación de peroxisomas, los daños hepatocelulares, la necrosis y la proliferación regenerativa y el trastorno del eje hipotálamo-hipófisis-testículos. Aunque el ser humano puede ser menos sensible a los tumores derivados de algunos de estos mecanismos, en conjunto en una evaluación del riesgo potencial para las personas no es posible descatar los tumores.

Los efectos críticos más importantes de una exposición breve aislada al HCFC-123, por ejemplo debido a la descarga de un extintor de incendios, son la depresión del sistema nervioso central y la mayor probabilidad de arritmia cardíaca inducida por la adrenalina. Los principales efectos derivados de una exposición repetida son las lesiones hepáticas, notificadas en trabajadores expuestos a concentraciones en el aire superiores a 5 ppm (31,1 mg/m^3) durante un período de 1 a 4 meses.