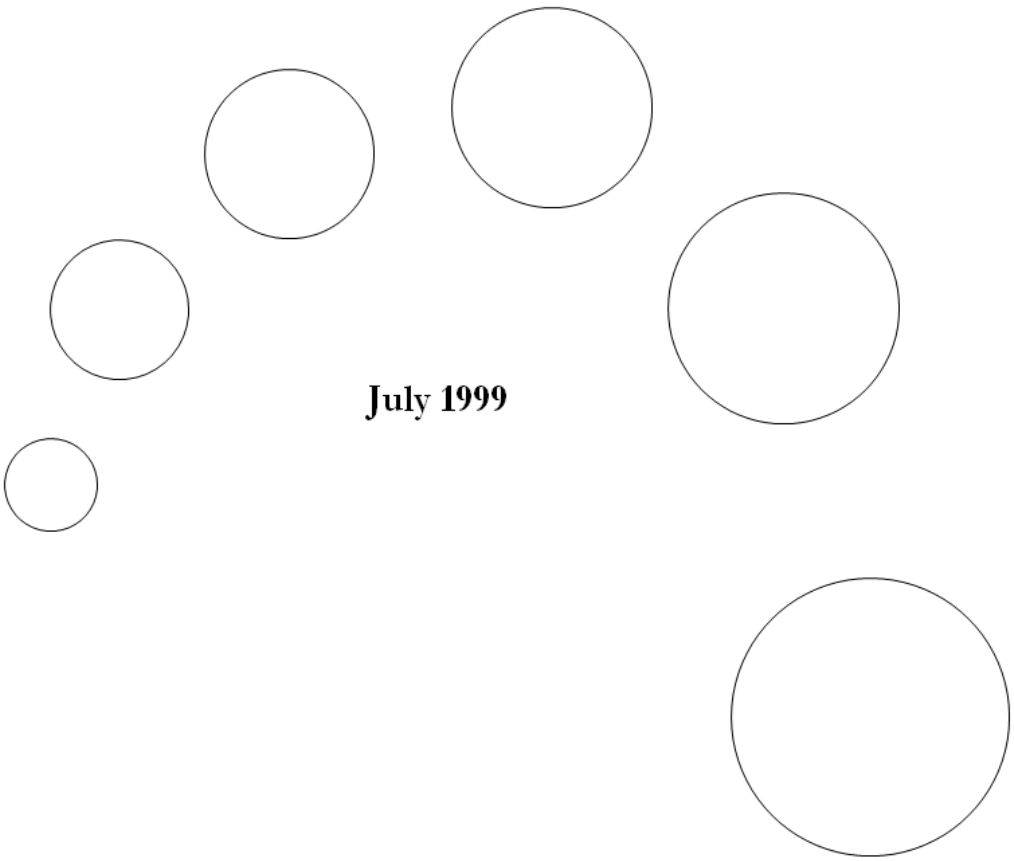
National Industrial Chemicals Notification and Assessment Scheme

2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) Priority Existing Chemical No. 4 Secondary Notification Assessment

Full Public Report



July 1999

ISBN 0 642 39968 9

Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals, by assessing the risks associated with these chemicals.

NICNAS is administered by the National Occupational Health and Safety Commission (NOHSC) and assessments are carried out in conjunction with Environment Australia (EA) and the Therapeutic Goods Administration (TGA), who carry out the environmental and public health assessments respectively. NICNAS has two major programs: one focusing on the risks associated with new chemicals prior to importation or manufacture; and the other focussing on existing chemicals already in use in Australia.

As there are many thousands of existing industrial chemicals in use in Australia, NICNAS has an established mechanism for prioritising and declaring chemicals as Priority Existing Chemicals (PECs). The assessment of the occupational health and safety, public health and environmental hazards of a PEC is based on information available at the time of declaration. Where further information becomes available after publication of a PEC report and/or where certain prescribed circumstances occur, as stipulated under Section 64(2) of the Act, the Director (Chemicals Notification and Assessment) may require a reassessment of the hazards of the PEC under secondary notification provisions (Division 6) of the Act.

This Full Public Secondary Notification Report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with the Act. Under Section 36 of the Act, applicants for secondary notification assessment were provided with a draft copy of the report for correction of errors and variation of content. Requests for corrections and variation of content were received from two applicants and a final report was prepared according to Section 37 of the Act. During all stages of preparation, the report has been subject to internal peer review by NICNAS, EA and TGA. Specific sections of this report were also peer reviewed by Dr I.L. Maclaine-cross, School of Mechanical and Manufacturing Engineering, University of New South Wales; consultant toxicologist, Professor J.G. McLean; and Clive Broadbent Associates Pty Ltd.

Under Section 40 of the Act, a public comment process is also undertaken for Secondary Notification Assessment Reports.

Under Section 64(2) of the Act, an introducer of HCFC-123 must inform the Director of any circumstances that may require a further assessment of risks to human health and the environment. For further details refer to Section 19 (Secondary Notification) in this report.

For the purposes of Section 78(1) of the Act, copies of Full Public Reports for New and Existing Chemical assessments, including secondary notification assessments, may be inspected by the public at the Library, National Occupational Health and Safety

Commission, 92-94 Parramatta Road, Camperdown, Sydney, NSW 2050 (between 10 am and 12 noon and 2 pm and 4 pm each weekday). Summary Reports are published in the *Commonwealth Chemical Gazette*, which are also available to the public at the above address.

Copies of this Full Public Secondary Notification Report and and the original PEC report (PEC4) are available free of charge from NICNAS at the following address:

GPO Box 58
Sydney
NSW 2001
AUSTRALIA
Tel: +61 (02) 9577 9437
Fax: +61 (02) 9577 9465 or +61 (02) 9577 9244

Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on PEC and New Chemical assessment programs;
- application forms for chemical assessment;
- subscription details for the NICNAS Handbook for Notifiers; and
- subscription details for the Commonwealth Chemical Gazette.

Information on NICNAS, together with other information on the management of workplace chemicals can be found on the NOHSC Web site:

http://www.worksafe.gov.au/worksafe/08/08_chem_ass.htm

Contents

LIST OF TABLES

LIST OF FIGURES

Abbreviations and Acronyms

ACTDG	Advisory Committee for the Transport of Dangerous Goods
ADG	Australian Dangerous Goods
AEL	allowable exposure limit
AFCAM	Association of Fluorocarbon Consumers and Manufacturers
AFEAS	Alternative Fluorocarbons Environmental Acceptability Study
AIHA	American Industrial Hygiene Association
ALD	approximate lethal dose
ALP	alkaline phosphatase
ALT	alanine transaminase
ANSI	American National Standards Institute
ANZECC	Australian and New Zealand Environment and Conservation Council
ARI	American Air Conditioning and Refrigeration Institute
AS	Australian Standard
AS/NZS	Australian/New Zealand Standard
ASHRAE	American Society of Heating, Refrigeration and Air Conditioning
AST	aspartate transaminase
BAT	Biologischer Arbeitsstoff Toleranz-Wert (Biological Tolerance Value)
CAS	Chemical Abstracts Services
CBIL	conjugated bilirubin
CCK	cholecystokinin
CFC	chlorofluorocarbon
CNS	central nervous system
CPI	cell proliferation index
DNA	deoxyribonucleic acid
EA	Environment Australia
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EEL	emergency exposure limit
EINECS	European Inventory of Existing Chemical Substances
EPA	Environment Protection Agency
FPAA	Fire Protection Association of Australia
FPIAA	Fire Protection Industry Association of Australia
FSH	follicle stimulating hormone
GGT	γ-glutamyl transferase
GWP	global warming potential
HCFC	hydrochlorofluorocarbon
hCG	human chorionic gonadotropin
ICDH	isocitrate dehydrogenase
IPCS	International Programme on Chemical Safety
ISO	International Organization for Standardization
LDH	lactate dehydrogenase
LH	luteinising hormone
LHRH	luteinising hormone releasing hormone
LOAEL	lowest observed adverse effect level

MAK	Maximale Arbeitsplatz Konzentration (Maximum Workplace Concentration)
MSDS	Material Safety Data Sheet
NADPH	the reduced form of nicotinamide-adenine dinucleotide phosphate
NFPA	National Fire Protection Association (US)
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute of Occupational Safety and Health (US)
NOAEL	no observed adverse effect level
NOHSC	National Occupational Health and Safety Commission
ODP	ozone-depleting potential
OECD	Organisation for Economic Cooperation and Development
PAFT	Program for Alternative Fluorocarbon Testing
PBPK	physiologically based pharmacokinetic model
POC	product of combustion
PPE	personal protective equipment
PRL	prolactin
RTECS	Registry of Toxic Effects of Chemical Substances
SCBA	self-contained breathing apparatus
SNAP	Significant New Alternatives Program
STEL	short term exposure limit
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TBIL	total bilirubin
TWA	time weighted average
UDS	unscheduled DNA synthesis
US EPA	United States Environmental Protection Agency
WEEL	workplace environmental exposure level

1. Introduction

19.1 Declaration and assessment as Priority Existing Chemical

The chemical 2,2-dichloro-1,1,1-trifluoroethane (CAS No. 306-83-2), known as hydrochlorofluorocarbon 123 or HCFC-123, was declared a Priority Existing Chemical (PEC) under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) on 1 June 1993. The reasons for declaration were the potential for a significant increase in occupational exposure to the chemical and release to the environment and its known toxicological effects, in particular, the induction of tumours in rats. Following the declaration of HCFC-123 as a PEC, three companies and one industry association applied for the assessment of the chemical.

A full public report (PEC4) on the assessment of HCFC-123 was published in March 1996 (NICNAS, 1996). The report concluded that HCFC-123 should be classified as a carcinogen in sub-category 3(b), signifying that further studies are necessary before a final decision on carcinogenic status can be made. It also made a number of recommendations to reduce potential risks to human health and the environment with respect to handling, use and disposal of the chemical, including a recommendation that the National Occupational Health and Safety Commission (NOHSC) develop an occupational exposure standard for HCFC-123.

In accordance with Section 62 of the Act, the publication of PEC4 revoked the declaration of HCFC-123 as a PEC. However, under Section 64(2) of the Act, an introducer of the chemical remained obligated to inform the Director (Chemicals Notification and Assessment) of any circumstances that might require a further assessment of risks to human health and the environment.

19.2 Secondary notification

In 1997, two introducers notified the Director of the availability of new information with regard to the adverse health effects of HCFC-123 which was considered sufficient to warrant a reassessment of its hazards and risks and in particular its carcinogenic hazard and cardiac sensitisation effect. As a consequence, notice was provided in the *Chemical Gazette* dated 2 September 1997 requiring reassessment of HCFC-123 under Section 65(2) of the Act and setting out the requirement under Section 65(3) of the Act that application for secondary notification be made by all persons who introduce HCFC-123 into Australia by import or manufacture.

Subsequently, secondary notification was given by six companies (see Section 3 below), two of which were also applicants for the assessment of HCFC-123 as a PEC. Four of the applicants for secondary notification assessment supplied additional toxicological and/or human health effects information with regard to the chemical. Three of them import HCFC-123 into Australia for use as a refrigerant, one imports the chemical in HCFC-blend fire extinguishants and one imports the chemical in a calibration gas. One company gave secondary

notification because it intended to import HCFC-123 (pure or in blends) for a new use, as a solvent in precision and electronics cleaning.[1]

1.2.1 Objectives

The objectives of this reassessment were to critically review new data and information made available since the publication of PEC4, particularly data of relevance to human health, and, where appropriate, revise the assessment of HCFC-123 as a PEC with regard to:

- the characterisation of the potential hazards of HCFC-123 to human health;
- the characterisation of the risk of adverse effects resulting from exposure to workers and the general public; and
- the recommendations to control exposures and/or reduce potential health risks.

1.2.2 Scope

This report presents a summary and evaluation of information which has been made available after the publication of PEC4 and is relevant to the reassessment of the potential health hazards from HCFC-123 exposure. Such information has either been submitted by applicants or obtained from a comprehensive literature survey or retrieved from other sources. Table 1 shows the areas in which new information was available for assessment and the sections in which the information can be found. NICNAS did not undertake any workplace site visits in connection with the preparation of this report.

Table 1 – Areas in which new information was available for assessment

Area	Section
Use and importation	7
Toxicokinetics and metabolism	9
Cardiac sensitisation	10.1.3
Endocrine effects	10.4.1; 10.5.2
Lactation effects	10.5.3
Human health effects	11.3
Mechanisms of tumour induction in rats	12.3.7
Exposure standards	14
Atmospheric breakdown products	15.1.3; 15.3

1.2.3 Format

For easy reference, the general format of this report follows that of PEC4. In sections with no or insignificant revisions, the reader is referred to PEC4 for a complete overview of the subject dealt with. The remaining sections are presented in their entirety and replace the corresponding sections of PEC4. In

[1] The overseas manufacturer subsequently withdrew the HCFC-123-based solvents from the market because of occupational health concerns and these products have not been introduced into Australia.

these sections, text and tables that have been revised are marked with a vertical line in the right-hand margin.

2. Background

2.1 The Montreal Protocol

Global concern over the depletion of the stratospheric ozone layer by chlorofluorocarbons (CFCs) and halons resulted in the Vienna Convention for the Protection of the Ozone Layer (adopted in March 1985) and its Montreal Protocol on Substances that Deplete the Ozone Layer (1987).

Under the Montreal Protocol, the production, import and export of halons, and CFCs, methyl chloroform and carbon tetrachloride, were totally phased out by 1994 and 1996 respectively, other than for a strictly limited range of essential uses approved by the parties to the Protocol. The Montreal Protocol does not prohibit the use of ozone-depleting substances beyond the phase-out date, but in Australia the use of halons has been restricted since late 1995.

The most recent amendment to the Montreal Protocol (Copenhagen Amendment 1992) regulates manufacture and import of hydrochlorofluorocarbons (HCFCs) with a total phase-out by 2020, with a very small amount able to be imported until 2030 to service existing equipment.

A total of 164 countries have signed the Montreal Protocol including Australia, which formally ratified the Copenhagen Amendment on 10 July 1994.

2.2 The Australian situation

In 1989 the Australian Environment Council (now the Australia and New Zealand Environment and Conservation Council - ANZECC) endorsed and published the *Strategy for Ozone Protection*. This document was developed by Commonwealth, State and Territory governments in association with industry, environmental and consumer groups.

The ANZECC *Revised Strategy for Ozone Protection in Australia* (ANZECC, 1994), which includes new information on technologies and chemical replacements for ozone-depleting substances, was published in April 1994. This strategy is compatible with the Montreal Protocol phase-out time line for CFCs and halons.

In Australia the phase-out of all ozone-depleting substances, including HCFCs, is brought about under the *Ozone Protection Act (1989)* (Cwlth) which was amended in 1995, and which is implemented by Environment Australia (EA).

In Australia, the phase-out of production, import and export of halons was achieved in 1993, a year in advance of the Montreal Protocol phase-out date. The use of halons was prohibited by 1996 under State and Territory legislation, and halon-filled fire extinguishing equipment is not permitted unless an Essential Use Permit is granted by the relevant State EPA. Similarly, the manufacture, import and export of all CFCs, methyl chloroform and carbon tetrachloride was phased

out by 1996, including the import and manufacture of certain products that contain or rely on these substances.

Early in 1995 the Commonwealth EPA released the summary paper *The Phase-out of Hydrochlorofluorocarbons in Australia* (EPA, 1995) in response to Recommendation 93/12 of the ANZECC *Revised Strategy for Ozone Protection in Australia*. This paper proposed amendments to the *Commonwealth Ozone Protection Act* which would phase-out the supply of HCFCs in Australia essentially by the end of 2015. A very limited supply would still be permitted until 2030 (or any earlier date set by the Montreal Protocol) primarily to service HCFC-based centrifugal chillers.

In line with the Montreal Protocol, a number of initiatives have been implemented in Australia to assist in the disposal and recycling of CFCs and halons such as the establishment of the Halon Bank, managed by DASCEM Holdings Pty Ltd, and the Ozone Depleting Substances Reclaim Fund, established by the Fluorocarbon Industry.

2.3 HCFCs as interim alternatives to CFCs and halons

The phase-out of the supply of CFCs and halons created an urgent need for acceptable substitute chemicals. Currently the most suitable replacements for many of the applications of these substances are partially halogenated chlorofluorocarbons (HCFCs).

Although the ozone-depleting and the global warming potential of HCFCs are considerably lower than those of their fully halogenated analogues (CFCs and halons), they are only being considered as interim (transitional) replacements until more acceptable alternatives are developed, for example, substances with zero ozone-depleting and global warming potential.

In Australia, HCFC-123 is currently being used as an interim replacement for CFC refrigerants (mainly CFC-11) and as a component of certain fire extinguishants introduced as interim replacements for Halons 1211 and 1301.

Under the US EPA Significant New Alternatives Program (US EPA, 1994a), HCFC-123 is regarded as an acceptable interim replacement for:

- CFC-11, CFC-12, CFC-500, and CFC-502 in industrial process refrigeration; and
- CFC-113 in precision cleaning.

HCFC-123 can act as a replacement in blends containing HCFC-123 as acceptable interim replacements for:

- sterilant blends containing CFC-12; and
- Halons 1211 and 1301 in fire suppression

Other uses for which HCFC-123 has been proposed overseas are as an expansion (blowing) agent in polyurethane foam manufacture and in solvent applications.

2.4 Scientific testing and assessment of CFC and halon alternatives

Some of the world's major CFC producing companies have co-operated to set up AFEAS and PAFT. The aim of these programs is to generate information on the

potential effects of CFC and halon alternatives on the environment and human health in order to promote safe, viable alternatives.

The first of several PAFT programs,[1] which included extensive toxicological testing of HCFC-123, was completed prior to the publication of PEC4 and the studies were made available for assessment.

Under NICNAS, HCFC-123 is the first CFC/halon alternative to be assessed as a Priority Existing Chemical (PEC) although a number of such alternatives have been notified and assessed as New Chemicals. These include the refrigerants HFC-32, HFC-143a, FC-218 and the extinguishants HFC-227ea, PFC-410 and FIC-13l1.

Reviews of HCFC-123 by international organisations have been carried out by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1996) and the International Programme on Chemical Safety (IPCS, 1992).

[1] PAFT 1, launched in 1987.

3. Applicants

Du Pont (Australia) Pty Ltd
168 Walker Street
North Sydney NSW 2060

MSA (Australia) Pty Ltd
137 Gilba Road
Girraween NSW 2145

Elf Atochem (Australia) Pty Ltd
5 Colquhoun Street
Rosehill NSW 2142

North American Fire Guardian Technology (Australia) Pty Ltd
Unit 5A
188 Canterbury Road
Canterbury NSW 2193

GSA Industries (Australia) Pty Ltd (Actrol Parts Division)[1]
19 King Street
Blackburn VIC 3130

Solvents Australia Pty Ltd[1]
77 Bassett Street
Mona Vale NSW 2103

[1] Joint applicants.

4. Chemical Identity

4.1 Chemical name

HCFC-123 is listed on the Australian Inventory of Chemical Substances (AICS) as *ethane, 2,2-dichloro-1,1,1-trifluoro-*.

CAS number	306-83-2
EINECS number	206-190-3
RTECS number	KI 1108000

4.2 Other names

CFC-123

1,1-Dichloro-2,2,2-trifluoroethane 2,2-

Dichloro-1,1,1-trifluoroethane

Dichlorotrifluoroethane

Dichloro(trifluoromethyl)methane FC-

123

Fluorocarbon 123 Freon-

123

Fron-123 Halon-

232 HCFC-123

Hydrochlorofluorocarbon 123

Propellant 123 R-

123

Refrigerant 123

Trifluorodichloroethane

4.3 Trade names

Pure substance

Asahiklin AK-123

Demeon 123

Environ 123

FE-232

Forane 123

Frigen

Genetron 123

Halotron HFA-

123

Solkaflam 123

Solkane 123

SUVA 123

Blends containing HCFC-123

The following blends are extinguishing agents. No refrigerant blends containing HCFC-123 are currently in use in Australia.

Halotron-I

HCFC-Blend A

HCFC-Blend C

HCFC-Blend D

NAF P-III

NAF S-III

4.4 Further information

For further information on the chemical identity of HCFC-123 (2,2-dichloro-1,1,1-trifluoroethane, CAS No. 306-83-2), see PEC4, Section 4.

5. Physical and Chemical Properties

HCFC-123 is a clear, colourless, non-flammable liquid with a slight ethereal odour. It boils at 27.6^{o}C and has a vapour density of 6.38 g/L (saturated vapour) and a vapour pressure of 89.3 kPa at 25^{o}C.

The conversion factors for HCFC-123 in air (at 25^{o}C) are 1 mg/m^{3} = 0.160 ppm and 1 ppm = 0.0001% = 6.25 mg/m^{3}.

Further details are provided in PEC4, Section 5.

6. Methods of Detection and Analysis

For an overview of methods of detection and analysis of HCFC-123, including monitoring and detection systems, see PEC 4, Section 6.

7. Use, Manufacture and Importation

7.1 Use

Design elementDesign elementIn Australia, the main use of HCFC-123 is as a refrigerant in low-pressure centrifugal chillers for air-conditioning systems as a technically suitable replacement for CFC-11. Smaller amounts of HCFC-123 are being used to replace CFC-12 in retrofitted high-pressure chillers.

Smaller, but significant amounts of HCFC-123 are used in the fire protection industry in fire extinguishant blends, which have been introduced to replace halon extinguishants. Two such blends currently imported into Australia are NAF S-III (HCFC Blend A) and NAF P-III (HCFC Blend C) which have been introduced to replace Halons 1301 and 1211 respectively. NAF S-III is being used as a 'total flooding agent' in fixed systems and NAF P-III as a 'streaming agent' in portable extinguishers. Both blends are particularly suitable for fires involving computer or electrical equipment. In addition, proposals are underway to use an extinguishant containing >90% HCFC-123 in military applications.

Trace amounts of HCFC-123 are being used to calibrate alarms or detectors in refrigeration plants.

Government authorities in other countries, notably the USA, have sanctioned the use of HCFC-123 for other purposes, including as an expansion (blowing) agent in polyurethane foam manufacture, in solvent applications and in sterilant blends.

7.2 Manufacture

HCFC-123 and extinguishant blends or calibration gases containing HCFC-123 are not manufactured in Australia, nor are there any plans to do so in the near future. Worldwide, commercially available volumes of the chemical may reach 10,000 t a year (AIHA, 1998).

7.3 Importation

HCFC-123 is imported into Australia either as a pure chemical or in fire extinguishant blends or pre-filled calibration gas cylinders. It is estimated that approximately 100 t of HCFC-123 (all uses) were imported from mid-1996 to mid-1998.

7.3.1 HCFC-123 refrigerant

Pure HCFC-123 is imported in heavy-duty steel drums, ranging in size from 45-300 kg. It is estimated that approximately 40 t of HCFC-123 were supplied to the air-conditioning market from mid-1997 to mid-1998. Because of a decline in the number of new chillers using HCFC-123, a major supplier of HCFC-123 predicts

a steady decline in total annual sales (all sources) for refrigerant from around 30 t in 2000 to approximately 3 t by 2008 (Du Pont, 1998).

7.3.2 HCFC-123 in extinguishant blends

NAF S-III and NAF P-III, which contain 4.75% and 60% HCFC-123 respectively, are imported into Australia in 1030 kg cylinders.

Imports of NAF S-III and NAF P-III, together with the HCFC-123 equivalent amounts are shown in Table 2.

Table 2 – Australian import volumes for extinguishant blends containing HCFC-123 (North American Fire Guardian Technology,1998)

Year	Extinguishant blend	Extinguishant (kg)	HCFC-123 (kg)
1996	NAF S-III	41,200	1957
1996	NAF P-III	41,200	24,720
1997	NAF S-III	nil	nil
1997	NAF P-III	nil	nil

Average yearly imports of HCFC-123 in extinguishant blends has increased more than 13-fold since 1994, with most of the rise accounted for by NAF P-III which is being used in portable extinguishers. Imports are expected to remain stable at 12-13 t of HCFC-123 equivalent per annum for some years and then decline as HCFCs are gradually being phased out.

7.3.3 HCFC-123 in calibration gases

HCFC-123 calibration gases are imported in small, pre-filled, pressurised cylinders containing 98 L of HCFC-123 in nitrogen at a concentration of either 30 or 100 ppm. Imports of cylinders total about a dozen a year, with a HCFC-123 equivalent of less than 1 g (MSA, 1998).

8. Exposure Assessment

There is the potential for environmental, occupational and public exposure to HCFC-123 resulting from its use as a refrigerant in centrifugal chillers in the air-conditioning industry and as an ingredient in extinguishants in the fire protection industry, with chiller maintenance work and firefighting being the main sources of exposure.

PEC4, Section 8 contains a full account of the human exposure data that were available in 1996.[1] Subsequently, several cases of occupational exposure to HCFC-123 have been reported that relate to the manufacture of heat-exchangers containing HCFC-123 and to the use of the chemical in vehicle air-conditioning systems and as a solvent degreaser. Although the chemical is not used for such applications in Australia, these cases have provided additional information on the human health effects of exposure to HCFC-123, which is included in Section 11.3.

[1] In PEC4, the results of HCFC-123 air monitoring from indoor discharge of Halotron extinguishants presented in Table 7 on page 25 are in ppm of HCFC-123.

9. Toxicokinetics and Metabolism

9.1 Animal studies

9.1.1 Absorption

Partition coefficients for HCFC-123 have been determined in various tissues (Dekant, 1993; Loizou et al., 1994; Vinegar et al., 1994). Results indicate lipophilic characteristics and as such absorption and distribution are expected to occur readily.

The uptake of ^{14}C-HCFC-123 from whole body inhalation exposure has been studied in both rats and guinea pigs (Dekant, 1993). The rate of uptake of HCFC-123 (ranging from 1000 to 5000 ppm) in rats (3-5 animals) was estimated by measuring the disappearance of radioactivity in a closed chamber study. In this study, uptake was reported to be saturated above 2000 ppm. In the study by Vinegar et al. (1994) uptake was biphasic with a rapid initial absorption during the first 30 min, followed by a slower rate of uptake. The author states that pharmacokinetic modelling of metabolic constants indicates a single saturable pathway.

In a supplementary study, two rats and two guinea pigs were exposed to two injections (into a closed recirculating exposure chamber) of 2000 ppm ^{14}C- HCFC-123 at 3-h intervals. Uptake of 50-60% of the applied radioactivity was estimated in rats and greater than 90% in guinea pigs (Dekant, 1993).

9.1.2 Distribution

The distribution of ^{14}C-HCFC-123 has been investigated in rats and guinea pigs following two injections (into a closed recirculating exposure chamber) of 2000 ppm ^{14}C-HCFC-123 at 3-h intervals (Dekant, 1993). After 48 h, around 2% of HCFC-123 was recovered in organs of rats and up to 6% in guinea pigs. In rats, the liver contained most of the radiolabelled HCFC-123, followed by testes, kidney, lung and brain, pancreas and spleen. A similar distribution profile was seen in guinea pigs.

9.1.3 Metabolism

Biotransformation

It has been estimated from uptake and elimination studies (in rats and guinea pigs) that around 25% of the absorbed dose of HCFC-123 undergoes biotransformation (Dekant, 1993; Harris et al., 1992). No significant differences were seen in the extent of HCFC-123 oxidation between microsomes from male and female rats (Urban et al., 1994).

Several *in vivo* and *in vitro* studies have clearly established that the major biotransformation product of HCFC-123 is trifluoroacetic acid (TFA) (Braeshear et al., 1992; Dekant, 1993; Dodd et al., 1993; Urban & Dekant, 1994). *In vitro*

studies in rat (and human) microsomes have shown that in the absence of NADPH or with the use of heat inactivated microsomes, TFA was not detected, indicating the involvement of cytochrome P-450 (Dekant, 1993; Urban et al., 1994). Moreover, evidence obtained from studies with diallyl sulphide, a selective mechanism-based inhibitor of CYP 2E1, indicates a major role for this isoform in the HCFC-123 biotransformation by the liver (Dekant, 1993; Urban et al., 1994). Other minor metabolites of HCFC-123 (detected in rat and guinea pig urine) were N-trifluoroacetyl-2-aminoethanol and N-acetyl-S-(2,2-dichloro-1,1-difluoroethyl)-L-cysteine. Chlorodifluoroacetic acid was detected *in vitro* (detected in rat and human liver microsomal fractions) but not *in vivo* in rats or guinea pigs.

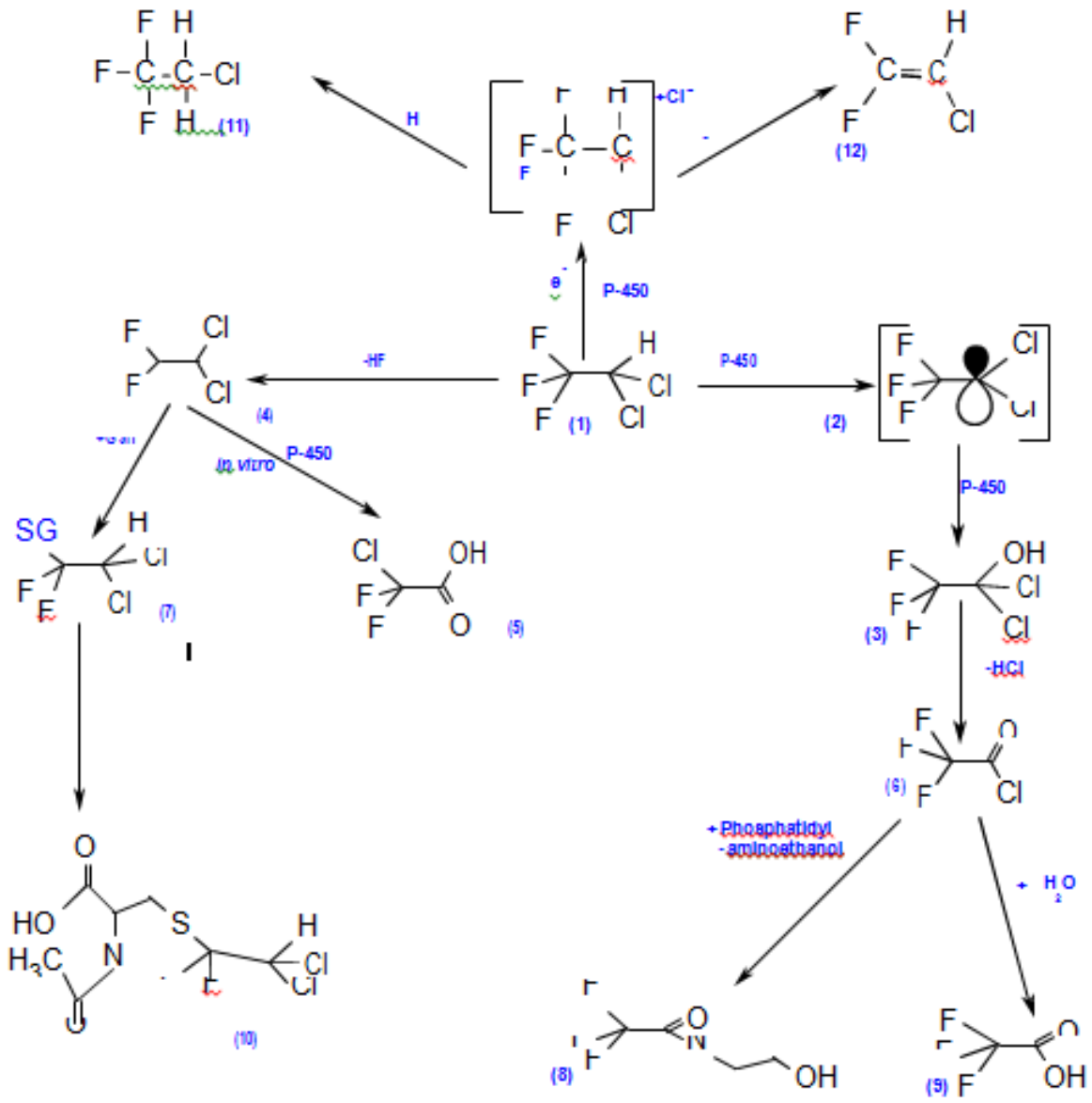
HCFC-123 has also been reported to undergo a cytochrome P-450 catalysed reductive metabolism in rats to form 2-chloro-1,1,1-trifluoroethane (HCFC-133a) and 2-chloro-1,1-difluoroethene (CDE) (Braeshear et al., 1992; Dodd et al., 1993). Trace amounts of both metabolites were found in liver, with HCFC-133a detected also in expired air and kidney (Braeshear et al., 1992). Both these reductive metabolites have also been identified *in vitro* but only under anaerobic conditions (less than 5% oxygen) (Godin et al., 1993; Urban et al., 1994). Reductive metabolites such as HCFC-133a and CDE may attack some types of cytochrome P-450 (isoforms 2E1 and 2B1/2) resulting in modification of the haem group and subsequent loss of enzymatic activity (Ferrara et al., 1997).

Metabolic studies indicate that the major biotransformation pathways for HCFC-123 is as shown in Figure 1 (Brashear et al., 1992; Dekant, 1993; Harris et al., 1992; Urban et al., 1994).

Studies on the rate of protein binding and TFA excretion in rats indicate that biotransformation of HCFC-123 is the rate-limiting pathway with respect to the observed saturation of these processes and that saturation occurs at exposures above 1000 ppm (Harris et al., 1992; Lewis, 1990). More recently, a study on blood levels of TFA in rats, indicated that HCFC-123 inhibits its own metabolism at high exposure levels, as a 50% decrease in peak blood levels of TFA (from approximately 90 to 40 mg/L) was seen between 1000 and 10,000 ppm HCFC-123 (Vinegar et al., 1994), a finding confirmed by Dodd et al. (1993). Metabolic rate constants developed for HCFC-123 in a PBPK model were K_m = 1.0 mg/L and V_{max} = 8.74 mg/kg/h (Brashear et al., 1992).

In lactating Rhesus monkeys exposed to 1000 ppm HCFC-123 for 6 h per day for 21 consecutive days, TFA was present in blood at concentrations that reached a maximum of 150-190 µg/mL after 2-3 weeks of exposure (Slauter, 1997).

Figure 1 - Major metabolic pathways for HCFC-123 as determined from *in vivo* and *in vitro* studies (adapted from Dekant (1993))



1.	HCFC-123
2.	1,1-Dichloro-2,2,2-trifluoroethylradical
3.	1,1-Dichloro-2,2,2-trifluoroethanol
4.	1,1-Dichloro-2,2-difluoroethene
5.	Chlorodifluoroacetic acid
6.	1,1,1-Trifluoroacetyl chloride
7.	Glutathione conjugate of 1,1-dichloro-2,2-difluoroethene
8.	N-trifluoroacetyl-2-aminoethanol
9.	Trifluoroacetic acid
10.	N-acetyl-S-(2,2-dichloro-1,1-difluoroethyl)-L-cysteine
11.	2-Chloro-1,1,1-trifluoroethane (HCFC-133a)
12.	2-Chloro-1,1-difluoroethene (CDE)

Protein binding

Binding of HCFC-123 metabolites to tissue proteins (including blood proteins) has been demonstrated in rats and guinea pigs (Dekant, 1993; Harris et al., 1992). Studies with HCFC-123 and structural analogues indicate that trifluoroacetylchloride (TFC) is the metabolite associated with this binding (Harris et al., 1992; IPCS, 1992).

The highest levels of protein binding have been detected in liver (Dekant, 1993) where N-trifluoroacetylated lysine adducts have been identified in microsomal and cytosolic proteins (Harris et al., 1992). The extent of binding to liver proteins in rats and guinea pigs exposed for 6 h to 2000 ppm HCFC-123 was 0.4-0.7 nmol HCFC-123 per mg protein (Dekant, 1993). Immunochemical detection of trifluoroacetylated liver proteins in rats exposed for 6 h to 100 ppm, 1000 ppm and 10,000 ppm HCFC-123 indicated that little binding occurred at 100 ppm and that the rate of adduct formation is saturated above 1000 ppm (Harris et al., 1992). Phenobarbitone pretreatment has been shown to increase the extent of hepatic protein binding in rats (Harris et al., 1992). In guinea pigs, glutathione depletion augmented binding of HCFC-123 metabolites to liver proteins (Lind et al., 1995).

Low levels of covalent binding of HCFC-123 metabolites were also detected in other organs of rats and guinea pigs (Dekant, 1993), including kidney, lung and brain following exposure to 2000 ppm HCFC-123 (the only level tested). In this study, covalent binding in testes and pancreas was reported as not being above background levels (Dekant, 1993).

9.1.4 Elimination and excretion

The main route of HCFC-123 elimination, based on inhalation data for other CFCs and halothane, is likely to be via exhalation as unchanged HCFC-123 (IPCS, 1992). In rats, steady-state expired breath concentrations of HCFC-123 were proportional to exposure concentrations at 100, 1000 and 10,000 ppm HCFC-123 and decreased rapidly on cessation of exposure, to around 10% of steady-state level 15 min post-exposure, indicating that exhalation is a major route of HCFC-123 elimination (Vinegar et al., 1994).

Similar studies by Dodd et al. (1993) and Vinegar et al. (1994) demonstrated that blood levels of HCFC-123 rapidly decreased (by about 90% in 2 h) when exposure ceased. The studies also showed that blood TFA levels continued to increase post-exposure (between 5-20 h) followed by slow elimination (estimated elimination half-life ($t_{1/2}$) of 2-4 h (Dodd et al., 1993)). Fat concentrations of HCFC-123 decreased by 98% between 1-8 h post-exposure (Vinegar et al., 1994). The data from this study clearly demonstrated that HCFC-123 from tissues other than blood contributed to blood TFA levels.

In a toxicokinetic pilot study in a single lactating Rhesus monkey exposed to 1000 ppm HCFC-123 6 h per day for 14 consecutive days, HCFC-123 was not detected in blood at any time, whereas the concentration of TFA fell from a maximum of 30 µg/mL approximately 30 min post-exposure to zero at 48 h, with an apparent elimination half-life of approximately 24 h (Slauter, 1997).

In rats, HCFC-123 is excreted in urine as TFA, N-acetyl-S-(2,2-dichloro-1,1-difluoroethyl)-L-cysteine, N-trifluoroacetyl-2-aminoethanol and inorganic

fluoride (Dekant, 1993). Approximately 25% of the estimated uptake was recovered in the urine during 48 h post-exposure of rats and guinea pigs to 2000 ppm ^{14}C-HCFC-123 (Dekant, 1993). Urinary excretion of TFA was increased or reduced by selective induction and inhibition of cytochrome P-450.

Vinegar et al. (1994) also demonstrated that the urinary TFA elimination rate in rats was linear up to 48 h post-exposure and that saturation occurred above 1000 ppm. Similar findings have been reported from other studies where urinary TFA elimination was saturated between 1000 and 4500 ppm (Lewis, 1990) and fluoride elimination saturated between 300 and 1000 ppm HCFC-123 (Malley, 1992).

Data from pharmacokinetic, biotransformation and urinary excretion studies indicate that hepatic elimination of TFA is the rate limiting step with respect to HCFC-123 metabolism (Dekant, 1993; Loizou et al., 1994; Vinegar et al., 1994). Rate constants for urinary TFA excretion in Sprague Dawley rats were K_m = 11.5 mg/L and V_{max} = 44.6 mg/kg/24hr for males and K_m = 3.7 mg/L and V_{max} = 35.5 mg/kg/24h for females (Dekant, 1993).

In lactating Sprague-Dawley (Crl:CD BR) rats and Rhesus monkeys exposed to 1000 ppm HCFC-123 for 6 h per day for 21 consecutive days TFA was excreted in milk at a maximum concentration of 65 µg/mL in the rat and 30 µg/mL in the monkey (Heinrich, 1996; Slauter, 1997). In monkeys, the milk also contained small, but detectable amounts (up to 5 µg/mL) of HCFC-123. In the rat study, milk was not analysed for HCFC-123.

9.2 Human studies

Limited data were available on the absorption, distribution, metabolic transformation or elimination of HCFC-123 in humans.

In an *in vivo* pilot study, four volunteers were exposed to inhalation of 60-73 ppm HCFC-123 for 6 h and their urine collected and analysed for TFA (Tanaka et al., 1998). Urine concentrations of TFA peaked at 10-27 mg/L 20-30 h post-exposure and returned to zero by 96 h post-exposure, with an estimated elimination half-life of approximately 25 h.

An *in vitro* study with human liver microsomes indicated that HCFC-123 is metabolised by cytochrome P450 enzymes, primarily by CYP 2E1 (Urban et al., 1994). The major biotransformation product was TFA. Chlorodifluoroacetic acid and inorganic fluoride were also identified in addition to a further (minor) uncharacterised metabolite. In this study significant variation existed in the rate of formation of TFA in liver samples from 7 subjects, which was directly related to the amount of CYP 2E1 protein present, but was neither age nor sex related. The rate of TFA formation by human liver microsomes was between 1.5 and 16 times faster than in rat microsomes (Dekant, 1993; Urban et al., 1994).

10. Effects on Experimental Animals and *in vitro* Bioassays

Toxicological studies made available for assessment have been evaluated and are summarised in this Section. Study protocols were assessed against OECD guidelines (OECD, 1981), the use of which are recommended in the NICNAS Handbook for Notifiers (NICNAS, 1999) and the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1998). Where studies were carried out in accordance with OECD guidelines, this has been noted as it provides some indication of the methodology. For all studies, results were considered valid provided the scientific quality and reporting of the data was considered adequate. Conclusions as to the significance of the findings with respect to potential human health effects and classification can be found in Section 12.

10.1 Acute toxicity studies

10.1.1 Oral toxicity

HCFC-123 was administered as a single dose (in corn oil by gavage) to male rats (ChR:CD), one animal per group, at doses ranging from 2250 to 11,000 mg/kg body weight (Henry, 1975). The approximate lethal dose (ALD[1]) was 9000 mg/kg body weight, where death occurred within 1 h. Rapid respiration and prostration were reported after oral administration of doses at and above 3400 mg/kg body weight. No effects were reported at the lowest dose level. Only a summary of the study was provided for assessment.

10.1.2 Dermal toxicity

Limit tests for dermal toxicity have been carried out in rats and rabbits according to OECD guideline No. 402 (Brock, 1988a, 1988b). HCFC-123 (>99% pure) was applied at a single dose of 2000 mg/kg body weight for 24 h to occluded, intact skin of 5 male and 5 female Crl:CD BR rats, and 5 male and 5 female New Zealand albino rabbits. Animals were observed for 14 days post-application. No animals died during these studies. Slight to moderate erythema was seen in rabbits (6 out of 10 animals) up to 5 days post- treatment. No gross pathological abnormalities were observed in either species.

[1] The lowest dose administered that causes mortality in at least one animal.

Table 3 - Summary of acute inhalation lethality studies

Test animal	*Exposure (ppm)*	*Duration*	*Mortality Ratio*	*Study end point, lethality*	*Clinical observations and pathology*	*Comments*	*Reference*
Rat (Albino)							
2 males/ group	12,500	30 min	0/2	LC_{50} (15 min) > 50,000 ppm	Incoordination, prostration, unconsciousness at all exposure levels. Congestion and oedema observed in lungs and kidneys of dead animals.	Purity of HCFC-123 only 71%. Animals (2) died up to 3 days following exposure.	Clayton (1964)
	25,000	15 min	0/2				
	50,000	15 min	0/2				
	100,000	2 min	2/2				
Mouse							
10 animals/ group	NR	30 min	NR	LC_{50} (30 min) = 74,000 ppm	No effects reported.	Experimental data not provided. Purity of test material not indicated. Sex and strain unspecified.	Raventos & Lemon (1965)
Rat (ChR:CD)							
6 males/ group	16,480 -18,900	4 h	0/6	LC_{50} (4 h) = 35,000 ppm	Immediate unresponsiveness, loss of balance, hyperaemia, irregular breathing, lacrimation and death at lethal exposure levels. Marked congestion in lungs, kidney, liver of dead animals.	Purity of test material (commercial grade) not indicated. Experimental data inadequate.	Clayton (1966)
	30,000 -40,500	4 h	2/6				
Rat (ChR:CD)							
6 males/ group	20,700	4 h	0/6	LC_{50} (4 h) = 32,000 ppm	Loss of mobility, lethargy, prostration, unresponsiveness and dyspnoea (effects reversible in surviving animals). No gross pathology or histopathology carried out.	Purity of test material not indicated.	Hall & Moore (1975)
	32,000	4 h	3/6				
	33,700	4 h	3/6				
	42,100	4 h	4/6				
	52,500	4 h	6/6				
	55,000	4 h	6/6				

Table 3 - Summary of acute inhalation lethality studies (cont.)

Test animal	*Exposure (ppm)*	*Duration*	*Mortality ratio*	*Study end point, lethality*	*Clinical observations and pathology*	*Comments*	*Reference*
Rat (ChR:COBS)							
10 males/ group	0	6 h	0/10	LC_{50} (4 h) = 52,640 ppm	Discolouration of lung, liver, thymus and small intestine seen at the highest 3 dose levels. Histopathology not reported.	Purity of test material not indicated.	Coate (1976)
	7,800	6 h	0/10				
	23,200	6 h	0/10				
	37,500	6 h	2/10				
	37,800	6 h	1/10				
	41,800	6 h	4/10				
	105,600	24 min	10/10				
	122,700	24 min	10/10				
Chinese hamster							
5 males/ group	10,000	4 h	0/5	LC_{50} (4 h) = 28,400 ppm	Muscular incoordination and prostation at all exposures. No gross or histopathological effects.	Protocol according to OECD 403. Purity of test material not indicated.	Darr (1981)
	14,000	4 h	0/5				
	22,000	4 h	0/5				
	26,000	4 h	0/5				
	31,000	4 h	5/5				

NR = Not reported

10.1.3 Inhalation toxicity

Lethality

A number of acute inhalation lethality studies for HCFC-123 have been carried out in rats, mice and hamsters, and are summarised in Table 3. The studies carried out in male rats indicate an LC_{50} (4 h) in the range 32,000 ppm to 53,000 ppm (Clayton, 1964; Clayton, 1966; Coate, 1976; Hall & Moore, 1975). Reversible CNS effects such as loss of mobility and balance, lethargy, prostration and dyspnoea were reported in the range 12,500 ppm to 42,000 ppm. A test carried out according to OECD guidelines (No. 403) in Chinese hamsters (males) indicates an LC_{50} (4 h) of 28,400 ppm (Darr, 1981). In this study, CNS effects (such as muscular incoordination and prostration) were seen at all exposure levels.

Liver effects

In an acute inhalation study, male Hartley guinea pigs (10 per group) were exposed to 0, 1000, 10,000, 20,000 and 30,000 ppm HCFC-123 for 4 h (Marit et al., 1994). All animals were sacrificed 48 h post-exposure. Histopathological lesions (seen in all exposure groups) were limited to the liver (no effects on kidney or heart) and included centrilobular and multifocal vacuolar fatty change, degeneration and necrosis. ICDH, ALT and AST were significantly increased in animals exhibiting severe effects. There was significant variation in the susceptibility to hepatotoxicity both within and between treatment groups and a clear dose-response relationship was not observed.

In a subsequent study by Lind et al. (1995) 24 male Hartley guinea pigs were exposed to 10,000 ppm HCFC-123 for 4 h and killed at either 10 or 96 h. Half of each group was injected 24 h before exposure with 0.8 g/kg of *l*-buthionine-(*S,R*)-sulfoximine to deplete hepatic glutathione. The animals killed at 10 h showed no differences between groups with respect to either ICDH or the gross appearance of liver tissue, but liver glutathione was considerably reduced in *l*-buthionine-(*S,R*)-sulfoximine treated animals. At 24, 48 and 72 h, ICDH was significantly increased in glutathione-depleted animals. At 96 h, there was minimal liver injury without glutathione depletion, whereas with depletion injury was marked to sub-massive in most animals. Glutathione depletion also augmented binding of HCFC-123 metabolites to liver proteins.

Behaviour

In an acute behavioural toxicity (inhalation) study (Mullin, 1976), Charles River:CD male rats (6 per group) were exposed to HCFC-123 at concentrations of 0, 1000, 2500, 5000 and 10,000 ppm for 1 h. The most sensitive effects elicited were failures in unconditioned reflexes (lift, grip and vertical bar). The estimated EC_{50} (1 h), for these effects was approximately 4000 ppm HCFC-123. No effects were observed at 2500 ppm. All effects were reversible with animals fully recovering within 24 h post-exposure.

Cardiac sensitisation

In an acute cardiac sensitisation study, groups of male Beagle dogs, pretreated with an intravenous injection of adrenaline (0.008 mg/kg), were exposed by inhalation (5 min) to HCFC-123 at concentrations of 10,300 ppm, 20,900 ppm and 40,600 ppm (Trochimowicz & Mullin, 1973). A challenge dose of adrenaline produced severe arrhythmia, ventricular fibrillation and cardiac arrest at the two highest concentrations (7 out of 9 animals) but no response was noted at the lowest exposure level. The EC_{50} (5 min) for cardiac sensitisation in dogs was calculated to be 19,000 ppm (119 g/m^3). CNS depression was observed at all exposure levels.

An acute cardiac sensitisation study in dogs has been conducted with the fire extinguishant NAF S-III, which is a blend of HCFC-22, HCFC-124 and HCFC-123 (Banks, 1997). Two groups of male Beagle dogs, pre-treated with an intravenous injection of adrenaline, were exposed by inhalation (5 min) to 12% and 14% NAF S-III. In 9 dogs exposed to 12% NAF S-III, a subsequent challenge dose of adrenaline (0.008 mg/kg) induced prolonged bursts of abnormal beats and brief fibrillation in 1 animal, prolonged bursts of abnormal beats in 6 animals and brief bursts or isolated occurrences of abnormal beats in 2 animals. In 10 dogs exposed to 14% NAF S-III, the adrenaline challenge dose induced persistent fibrillation and death in 1 animal, prolonged bursts of abnormal beats and brief fibrillation in 1 animal, prolonged bursts of abnormal beats in 7 animals and brief bursts of abnormal beats in 1 animal.

10.2 Irritation studies

10.2.1 Skin irritation

HCFC-123 (pure) was evaluated for skin irritation potential in male and female New Zealand albino rabbits (Brock, 1988c). The study was carried out according to OECD guideline No. 404. No erythema or oedema were observed up to 72 h following occlusion (4 h) of intact skin with 0.5 mL (730 mg) of HCFC-123. The sensitivity of this study was confirmed by a positive control substance.

10.2.2 Eye irritation

The potential for HCFC-123 to induce eye irritation was investigated in albino rabbits, sex and strain unspecified (Britelli, 1975). HCFC-123, as 0.1 mL of undiluted or 0.2 mL of 50% HCFC-123 in propylene glycol, or 0.1 mL of pure propylene glycol, was placed in the conjunctival sac of the right eye of two animals. After 20 seconds the treated eye of one animal in each group was washed with water for 1 min. Observations of the cornea, iris and conjunctiva were made after 1 and 4 h, and at days 1, 2, 3, 7 and 14.

In the animals treated with undiluted HCFC-123, mild to moderate conjunctival irritation (washed and unwashed eye) and mild to slight corneal opacity (washed eye only) were observed up to 3 days after dosing. Similar effects were seen in animals treated with 50% HCFC-123 in propylene glycol, except that moderate to severe conjunctival irritation was seen in unwashed eyes and moderate corneal opacity was observed in the unwashed eye. Propylene glycol *per se* had no effect on the cornea or iris (washed or unwashed eye) but did elicit mild to slight

conjunctival irritation (washed and unwashed eye). Although this study did not conform to OECD test guidelines it was considered adequate.

10.3 Skin sensitisation study

The sensitisation potential of HCFC-123 was tested in a group of 10 male albino guinea pigs (Goodman, 1975). In the induction stage of the test, 0.1 mL of a 1% solution of HCFC-123 in dimethyl phthalate was administered by intradermal injection once a week for 3 weeks. Two weeks after the final injection the animals were challenged with an application (0.05 mL) of 10% (approximately 7 mg HCFC-123) and 50% (approximately 35 mg HCFC-123) HCFC-123 in propylene glycol vehicle to intact shoulder skin. No signs of sensitisation were seen 48 h after challenge and no signs of irritation were evident during the study.

10.4 Repeated dose (inhalation) studies

10.4.1 Subacute (5-28 days) toxicity

Several short-term repeated dose inhalation studies have been performed in rats, with an additional study in guinea pigs, summaries of which are presented in Table 4. In each case, HCFC-123 was administered for 6 h per day, 5 days per week, for 2-4 weeks at concentrations ranging 1000-20,000 ppm.

The main target organs for HCFC-123-elicited effects in these studies were the CNS, liver and testes. CNS effects were seen at and above 5000 ppm and were reversible overnight. In rats, HCFC-123 caused increased liver to bodyweight ratio, depressed serum triglyceride, cholesterol and glucose levels (Warheit, 1993); elevated serum AST, ALT and ALP activities (Kelly, 1975; Kelly, 1989); increased ß-oxidation activity (Warheit, 1993); hepatic centrilobular fatty change (Kelly, 1989; Warheit, 1993); hepatocyte hypertrophy (Warheit, 1993); increases in the number of hepatic mitochondria and peroxisomes and an increase in hepatocyte mitotic activity, that is, cell proliferation index (CPI) (Warheit, 1993). Changes in hepatic morphology and serum biochemistry developed at 1000 ppm, and changes in most parameters were dose-related. Levels of ß-oxidation activity, increased peroxisome numbers and changes in hepatic morphology (weight and cellular changes) indicate that HCFC-123 is a mild peroxisome proliferating compound in rats. Species differences in toxicity were evidenced by the lack of peroxisome proliferation and decreased liver weight in guinea pigs. In addition guinea pigs developed hepatocyte necrosis as opposed to hypertrophy (in rats) (Warheit, 1993).

In rats, increased testes weights were observed at 1000 ppm HCFC-123, together with elevated serum androgen concentrations, Leydig cell hyperplasia (1 animal only), seminiferous tubule atrophy and degeneration, epididymal hypospermia and germinal cell necrosis at exposure levels greater than 18,000 ppm. Testicular effects were not seen in guinea pigs. Testicular peroxisome proliferation was not reported in any of the studies assessed.

A slight increase in pancreatic peroxisome proliferation was seen in guinea pigs, however no changes in pancreatic peroxisome proliferation were seen in rats or guinea pigs exposed to the WY-14643 (known peroxisome proliferator) which serves to question the significance of this finding. Similarly, the slight decrease in

pancreatic peroxisome proliferation seen in rats in the same study was not considered biologically significant (Warheit, 1993). Slight increases in pancreatic mitotic activity (CPI) were seen in both species, although no changes in pancreas morphology were seen. In the same study, insulin levels were statistically decreased in rats exposed to HCFC-123. This finding was considered to be a physiological response to decreased glucose levels rather than an indicator of diminished pancreatic function, although data for WY-14643 confound this conclusion (Warheit, 1993).

The study in rats and guinea pigs by Warheit (1993) was devised as a follow-up mechanistic study to the 2-year (chronic inhalation) study, carried out by Malley (1992) (see Section 10.4.3). This study is discussed in more detail in Section 12.3.7 on carcinogen hazard assessment.

More recently, two short-term, repeated dose inhalation studies have compared the gross pathological, clinical, biochemical and/or endocrine effects of HCFC-123 in rats to those of HFC-134a and HCFC-141b.

In a biochemical study in male rats, decreased body weight gain, depressed serum triglyceride and cholesterol levels and increased hepatic peroxisome activity were evident after 5 days of exposure to 5400 ppm HCFC-123 (Keller, 1995).

In an endocrinological study carried out according to OECD guideline No. 412, groups of male and female rats were exposed to either 5200 ppm HCFC-123, 21,400 ppm HCFC-141a or 47,900 ppm HFC 134a for 6 h per day for 14 consecutive days (Hofmann, 1995; Sandow et al., 1995a). Whereas no toxic effects were detected in animals exposed to HFC-134a or HCFC-141b, exposure to HCFC-123 caused staggering gait and sleepiness, decrease of body weight (females only), decrease in absolute kidney, ovary and pituitary weights in females and increased liver to body weight ratio in males. During the study, basal and stimulated sex hormone levels (LH, FSH, prolactin and testosterone in males) were determined. Stimulants used were mono-iodo-tyrosin on day 10 and buserelin on day 14. Mono-iodo-tyrosin releases prolactin from the pituitary gland, whereas buserelin is a synthetic gonadotropin-releasing hormone. After the last exposure, pituitary LH, FSH and prolactin content and LHRH receptor quantity were determined and testes and ovaries were analysed for testosterone and oestradiol/progesterone levels respectively. In male rats, the prolactin response after mono-iodo-tyrosin, the testosterone response after buserelin and the testicular testosterone content were reduced in all test groups. In female rats, there was an enhanced FSH/LH response after buserelin in animals exposed to HCFC-123 and HCFC-141b. Pituitary content of FSH declined after exposure to HCFC-123 and HFC-134a, but increased after HCFC-141b. Pituitary prolactin content was reduced in all test groups.

Table 4 - Summary of subacute inhalation toxicity studies

Test animal	*Exposure protocol*	*Duration*	*Gross observations/ body & organ weights*	*Clinical and pathological effects*	*Comments*	*Reference*
Rat (ChR:CD)						
10 males/group	0 and 9,100-9,700 ppm (measured concentration)	6 h per day, 5 days per week, for **2 weeks**	Loss of motor coordination; unresponsive to noise. Kidney weight (rs+)*.	No effects on blood chemistry except AST (s+)* at end of study and 14 days post-exposure. Histopathology – unremarkable.	Purity of test material not indicated. Clinical and pathological tests carried out on 5 animals at end of study and 14 days post-exposure.	(1) Kelly (1975) (2) Trochimowicz et al. (1977)
Rat (Crl:CD BR)						
10 males & 10 females/group	0, 1,000 [a], 5,000[b], 10,000[c] and 20,000[d] ppm (approximate concentrations)	6 h per day, 5 days per week, for **4 weeks**	Anaesthetic effects (e.g. unresponsive to noise) in [b] [c] & [d] (dose related). Body weights (-) in all test groups (dose related in males) and (s-)* in [c] & [d]. Liver weight (rs+)* in all test grps (females - dose related) (rs+)* in [d] males. Testes weight (rs+)* in [a] [c] & [d].	Degeneration (uni & bi) of seminiferous tubules and epididymal hypospermia in 6/10 animals in [d] (cf 2/20 control animals). Liver Cyt-P450 (s-)* in all female test grps and in [b] [c] & [d] in males (dose related). Plasma AST (s+)* in [c] & [d] males, ALT (s+)* in [d] males. Urinary fluoride (+) in all grps (s+)* in [d] both sexes & [c] females.	Protocol according to OECD 412. Animals recovered from anaesthetic effects overnight. Hepatic fatty change seen in test animals (12% of test animals) was not dose related and was not considered biologically significant. Testicular lesions seen in animals exposed to 20,000 ppm were reported as moderate to severe whereas in controls these lesions were reported as minimal to moderate. No biologically significant changes seen in cytochrome b5 activity.	Kelly (1989)
Rat (CD BR)						
6 males/group	0, 977 [a], 4,510[b], 19,500[c] ppm (measured concentrations)	6 h per day, 5 days per week, for **4 weeks**	Anaesthetic effects in [c]. Body weights (-) in all test groups. Liver weight (as+)* (rs+)** in [c]. Testes weight (rs+)* in all test grps.	Hepatocyte hypertrophy & centrilobular fatty change in all test grps. Peroxisome and mitochondria prolif (s+)** in [b] & [c]. SER (s-)** in [b] & [c] (all dose related). Plasma AST (s+)** in all test grps, ALT (s+)* in [a] & [c], ALP (s+)** in [c], trig (s-)** in all test grps, chol (s-)** in [b] & [c].	Protocol according to OECD 412. TFA measured in urine. Leydig cell hyperplasia, tubular atrophy and epididymal hypospermia seen in 1/6 animals in [c]. No biologically significant changes seen in Liver Cyt-P450 and cytochrome b5 activity. Beta-oxidation activity (towards palmitoyl CoA) = 1.9, 2.0 & 3.3 times control levels in [a] [b] & [c] respectively.	Lewis (1990)

Table 4 - Summary of subacute inhalation toxicity studies (cont.)

Test animal	*Exposure protocol*	*Duration*	*Gross observations/ body & organ weights*	*Clinical and pathological effects*	*Comments*	*Reference*
Rat (Crl:CD BR)						
17 males/group	0 and 18,200 ppm (mean exposure level)	6 h per day, 5 days per week, for **4 weeks**	Body weights(s-)*. Liver weight (rs+)*. Testes weight (as+)(rs+)*. ASO (as-)*.	Hepatocellular hypertrophy (+) in all test animals. Atrophy (uni & bi) of seminiferous tubules in 3/5 animals. Germinal cell necrosis & syn/sl in 4/5 animals. Liver peroxisome prolif & CPI (s+)*. Trig/Chol/Gluc/Ins (s-)*. CCK/Oestradiol/Test(+).	Peroxisome proliferation assay not carried out with testicular tissue. Liver peroxisome prolif measured by ß-oxidation activity (towards palmitoyl CoA) - 4.7 times control levels. LH also measured - no change from controls. Although reported as not statistically significant, testosterone levels were 50% higher than controls.	Warheit (1993)
Rat (Crl:CD BR)						
5 males/group†	0, 5400 ppm (mean exposure level)	6 h per day for **5 days**	Body weight gain (s-)*. Liver weight (as-)* (rs-)*.	Serum cholesterol (s-)*. Serum triglycerides (s-)*.	Liver peroxisome β-oxidation activity 2.9 times control levels*.	Keller (1995)
Rat (Crl:CD BR)						
10 males & 10 females/group†	0, 5200 ppm (mean exposure level)	6 h per day for **14 days**	Staggering gait; sleepiness. Liver weight (rs-)* in males. Body weight (s-)*, kidney, ovary and pituitary weights (as-)* in females.	Serum PRL response to mono-iodo-tyrosin (s-)*, serum test response to buserelin (s-)* and testis test content (s-)* in males. Pituitary FSH (s-)* and PRL (s-)*, serum FSH response to buserelin (s+)* in females.		(1) Hofmann (1995) (2) Sandow et al. (1995a)
Guinea pig (Hartley - BR VAF/PLUS)						
17 males/group	0 and 9,400 ppm (mean exposure level)	6 h per day, 5 days per week, for **4 weeks**	Body weights(s-)*. Liver weight (as-)(rs+)*. Testes (as-)*. ASO (as-)(rs-)*.	Centrilobular fatty change (+) in all test animals. Hepatocyte necrosis (+) in 3/5 animals. No testicular lesions. Testes CPI (+). Liver peroxisome prolif (-) CPI (+). Trig/Chol/Gluc/Ins (s-)*. Serum CCK/Test (-)	Although reported as not stat. significant, testosterone levels were 50% lower than controls. Initial exposure level for HCFC-123 was 20,000 ppm. Level was reduced to 9,400 ppm due to severe weight loss. Three treated guinea pigs died during study.	Warheit (1993)

*	*P ≤ 0.05*	*ALP*	*Alkaline phosphatase*	*FSH*	*Follicle stimulating hormone*	*s*	*Statistically signifcant*
**	*P ≤ 0.*	*ALT*	*Alanine transaminase*	*Gluc*	*Glucose*	*syn/sl*	*Syncytial sloughing*
†	*Only animals exposed to HCFC-123*	*ASO*	*Accessory sex organs*	*Ins*	*Insulin*	*SER*	*Smooth endoplasmic reticulum*
+	*Increase*	*AST*	*Aspartate transaminas*	*LH*	*Luteinising hormone*	*test*	*Testosterone*
-	*Decrease*	*CCK*	*Cholecystokinin*	*PRL*	*Prolactin*	*TFA*	*Trifluoroacetic acid*
a	*Absolute weight*	*Chol*	*Cholesterol*	*prolif*	*Proliferation*	*trig*	*Trigycerides*
[a], [b] etc	*Test group designations*	*CPI*	*Cell proliferation index*	*r*	*Relative weight*	*uni & bi*	*Unilateral & bilateral*

10.4.2 Subchronic (90 days) toxicity

A number of subchronic inhalation studies have been carried out in rats and dogs and are summarised in Table 5. In each case, HCFC-123 was administered for 6 h per day, 5 days per week at concentrations ranging between 300 and 10,000 ppm.

The main effects seen in these studies were CNS depression and liver injury, with limited evidence of effects on kidney function.

Reversible CNS effects were recorded in both species at and above 1000 ppm. Neurobehavioural screening (including grip strength, landing foot splay, startle response, tail pinch and righting reflex) showed no treatment related effects in a neurotoxicity study (Coombs, 1994) except a statistically significant reduction in arousal at 1000 and 5000 ppm HCFC-123. No treatment-related effects on the brain or nerve tissues were revealed by histological examination.

In 90-day studies in rats, HCFC-123 caused dose-related increases in liver weight at the lowest level tested (300 ppm) together with hepatocyte atrophy, focal necrosis (in males) and mixed cell inflammation at and above 500 ppm. Levels of ß-oxidation activity, increased peroxisome numbers (measured at 5000 ppm only) and changes in hepatic morphology (weight and cellular changes) indicate that HCFC-123 is a mild peroxisome proliferating compound in this species. Significant elevations in serum ALT, AST and ALP activities were seen at 1000 ppm in two rat studies, however the absence of hepatic histopathological changes in these studies serve to question the biological significance of these enzyme increases. Significant decreases in serum triglyceride and glucose levels were also seen at 1000 ppm in all test groups in addition to decreases in serum cholesterol in females (Brewer & Smith, 1977a; Doleba-Crowe, 1978; Malley, 1990). Dogs also displayed elevated ALP activities at and above 1000 ppm and elevated AST, ALT and liver discolouration, hypertrophy, and necrosis at 10,000 ppm (Doleba-Crowe, 1978).

Relative kidney weights were increased in female rats at 1000 ppm, accompanied by elevated blood urea nitrogen (BUN) levels (in males and females). BUN levels were also significantly increased in dogs exposed to 10,000 ppm (Doleba-Crowe, 1978). Although statistically increased, the biological significance of increased BUN levels was questioned by study authors as changes were reported to be within the range of normal variation.

Testicular weights were increased in rats at 300 ppm and above. Severe hypospermia and unilateral tubular atrophy was seen in a single rat exposed to 5000 ppm (Malley, 1990).

Table 5 - Summary of subchronic inhalation toxicity studies

Test animal	*Exposure protocol*	*Duration*	*Gross observations/ body & organ weights*	*Clinical and pathological effects*	*Comments*	*Reference*
Rat (ChR) Albino						
35 males & 25 females/group	0 500[a] 1,000[b] 5,000[c] ppm	6 h per day 5 days per week for 90 days	Body weights (s-)** in [c] males & in [b] & [c] females. Liver weight (rs+)* in all test groups (females) & in [c] males. Adrenal weight (as-)* in [b] males. Kidney weight (as-)* (rs+)* in [c] female & (as-)* in all test groups (males).	Mild focal necrosis (+) in all males & (+) in [a] & [b] females; MCI (+) in all test groups. Hepatocyte atrophy / tel [+] in all males & in [c] females. Gluc (-) in [a] & [b] females.	Purity of test material not indicated. Serum insulin in male animals returned to normal range 30 days post-exposure. Urinary fluoride (+) in [b] males & (+) in all test groups (females). 10 male & 5 female animals were allowed 30 days recovery period at end of study. In these groups no significant differences were seen in body / organ weights or in terminal histopathology (except MCI seen in [c] females).	Brewer & Smith (1977a)
Rat (ChR:CD)						
27 males & 27 females/group	0, 1,000[a] 10,000[b] ppm	6 h per day 5 days per week for 90 days	Anaesthetic effects (e.g. lack of motor coordination & unresponsiveness) in [b]. Body weights (-) in both test groups. Liver weight (as+)(rs+)* in both test groups. Testes weight (r+) in both test groups. Adrenal weight (r+) in both test groups (male). Kidney weight (r+) in both test groups (female).	Histopathology – unremarkable. AST (s+)* in both test groups (males); ALT (s+)* in males in [a]; ALP (+) in both test groups (males) & (+) in [b] females; LDH (+) in [b]. BUN (s+)* in both test groups (males) & in [a] females; Gluc (s-)* in both test groups (female) & in [b] males; Prot (s-)* in both test groups.	Animals recovered from anaesthetic effects 15-30 min post-exposure. Histopathology carried out on 6 animals per test group. Only summary of results available for assessment. Lower organ to body weight in testes; adrenal and kidney may reflect lower body weights. Urinary fluoride (+) in both test groups.	Doleba-Crowe (1978)
Dog (Beagle)						
4 males/group	0 1,000[a] 10,000[b] ppm	6 h per day 5 days per week for 90 days	Anaesthetic effects (e.g. lack of motor coordination & unresponsiveness) in [b].	Gross histopathology - discolouration of livers in [b]. Hepatic hypertrophy, necrosis and inflammatory cell infiltration in [b]. AST (+) in [b]; ALT (+) in [b]; ALP (s+)* in both test groups. BUN (+) in [a] & (s+)* in [b]; Gluc (+) in both test groups.	Animals recovered from anaesthetic effects 15-30 min post-exposure. Only summary of results available for assessment. No compound related pathological effects were seen at 1000 ppm.	Doleba-Crowe (1978)

Table 5 - Summary of subchronic inhalation toxicity studies (cont.)

Test animal	*Exposure protocol*	*Duration*	*Gross observations/ body & organ weights*	*Clinical and pathological effects*	*Comments*	*Reference*
Rat (Crl:CD BR)						
10 males & 10 females/group	0 300[a] 1,000[b] 5,000[c] ppm	6 h per day 5 days per week for 90 days	Anaesthetic effects (e.g. unresponsive to noise) in [c]. Body weights (-) in [b] & [c]. Liver weight (rs+)* in [b} & [c] and [a] females. Testes weight (r+) in all test groups.	Histopathology – unremarkable. Hepatic peroxisome prolif (s+)* in all test groups (female) & in [b] & [c] males. Trig/Gluc (s-)* in all test groups; Chol (s-)* in [b] & [c] females. BUN (s+)* in [b] & [c] both sexes & in [a] females. AST (s+)* in [b] & [c] males & (-) in all test groups (females); ALT (s+)* in [b] & [c] males & (-) in all test groups (females); ALP (s+)* in [b] & [c] males; LDH (s+)* in [c] males. Urinary fluoride (+) in all test groups & (s+)* in all test groups (male) & [c] female.	Animals recovered from anaesthetic effects overnight. Body weight gain (s+)* in all test group (females) up to test day 48. Severe hypospermia & unilateral tubular atrophy seen in 1/10 animals at 5000 ppm. Liver peroxisome prolif measured by ß-oxidation activity (towards palmitoyl CoA) and electron microscopy in [c] test groups. ß-oxidation activity in males = 1.9, 3.4 & 3.7 and females = 2.6, 2.2 & 2.4 times control levels in [a] [b] & [c] respectively.	Malley (1990)
Rat (Sprague-Dawley CD)						
10 males & 10 females/group (neurotoxicity study)	0 300[a] 1000[b] 5000[c] ppm	6 h per day 5 days per week for 13 weeks	Anaesthetic effects (half & fully closed eyes) in [b] & [c]. Behavioural changes (lower arousal) in [b] & [c] males. Bodyweights (s-)* in [b] & [c] in females from week 2 onwards. Relative brain weight – unaffected.	Histology of brain, medulla/pons, cerebellar cortex, spinal cord, ganglia, dorsal and ventral root fibres and peripheral nerves (sciatic, sural and tibial) was unremarkable. No other tissues were examined.	Behavioural changes did not increase in severity with time, and disappeared during recovery period (weeks 13 to 17). Body weights increased following withdrawal of treatment. There were no effects on food consumption.	Coombs (1994)

*	*P≤0.05*	*AST*	*Aspartate transaminase*	*Prot*	*Total protein*
**	*P≤0.01*	*BUN*	*Blood urea nitrogen*	*r*	*Relative weight*
+	*Increase*	*Chol*	*Cholesterol*	*s*	*Statistically significant*
-	*Decrease*	*Gluc*	*Glucose*	*Tel*	*Telangiectasis*
[a], [b] etc	*Test group designations*	*Ins*	*Insulin*	*TFA*	*Trifluoroacetic acid*
a	*Absolute weight*	*LDH*	*Lactate dehydrogenase*	*Trig*	*Triglycerides*
ALP	*Alkaline phosphatase*	*MCI*	*Mixed cell inflammation*		
ALT	*Alanine transaminase*	*Prolif*	*Proliferation*		

10.4.3 Chronic (2 years) toxicity

A combined chronic inhalation toxicity/oncogenicity study was carried out by Malley (1992). Crl:CD BR rats (80/sex/group) were exposed to 0, 300, 1000 and 5000 ppm (0, 2, 6, 31 g/m^3) HCFC-123 for 6 h per day, 5 days per week for 24 months. The purity of the test material was reported to be 99.8%. The study was carried out according to OECD guideline No. 453.

In this study, serum biochemistry was carried out at 6, 12, 18 and 24 months and histopathology at 12 and 24 months. Historical oncogenicity data for Charles River (Sprague-Dawley) rats, obtained from the performing laboratory was used for comparative purposes.

The main target organs for treatment related effects in this study were the liver, testes and pancreas. The incidence of tumours in these organs is summarised in Table 6.

Hepatic effects

Perturbations in serum biochemistry (carried out on groups of 20 rats per sex at 6-month intervals) were inconclusive with respect to diagnosis of hepatocellular dysfunction. Although elevations were seen in serum ALP, ALT and AST activities (highest at 5000 ppm HCFC-123), increases were considered to be within normal biological variation. Similarly, significant decreases in serum triglycerides, cholesterol and glucose levels (seen at 12 and 18 months) may be related to the hypolipidaemic potential of HCFC-123 rather than to overt liver dysfunction.

Groups of 5 rats per sex were assessed for hepatocellular proliferation (CPI) and peroxisome proliferation at 12 months. Treatment related differences in mitotic activity (CPI) were not observed at 5000 ppm and hence other test groups were not evaluated. A dose-related increase in hepatic peroxisome proliferation (as assessed by increased ß-oxidation enzyme activity) was seen in male rats with increases of 2.3-, 3.1- and 4.0-fold at 300, 1000 and 5000 ppm HCFC-123 respectively. In females, significant increases were only seen at the two highest doses, where 1.7- and 3.1-fold increases were measured. The smaller increases in female rats may be due to the unusually high ß-oxidation activity in controls.

No compound-related gross or microscopic changes were observed at any exposure level in either males or females at 12 months.

At 24 months exposure to 5000 ppm HCFC-123, liver weights were significantly increased and accompanied by discolouration and hepatic masses in both sexes. Histopathology revealed a number of treatment-related effects including cystic degeneration and cellular alteration at 1000 and 5000 ppm, cholangiofibrosis (females), necrosis (males), centrilobular fatty change, biliary hyperplasia and ectasia at 5000 ppm.

At 24 months significant increases in the incidence of hepatocellular adenomas (both sexes) and cholangiofibromas (females) were seen at the highest exposure level, although a significant increase in hepatocellular adenomas was also seen in females at 300 ppm (see Table 6). No increase in hepatic tumours was seen at 12 months. Increases in certain malignant tumours were also seen at 24 months but

were either metastatic in origin or similar to historical controls and therefore not considered compound related.

Testicular effects

Testicular weights were increased at 24 months at all exposure levels, but were not statistically greater than controls. Male rats exhibited dose-related increases in unilateral seminiferous tubular atrophy and focal interstitial (Leydig) cell hyperplasia, significant at 5000 ppm and 1000 ppm respectively. Epididymal hypospermia occurred at 5000 ppm HCFC-123.

Although increases were also seen in Leydig (interstitial) cell adenomas, especially bilateral adenomas at all exposure levels, a dose-response relationship was not observed (see Table 6), and statistical significance was only seen at 5000 ppm, although when the tumour types are combined, significance is seen at all exposure levels. Malignant neurofibrosarcoma seen in a single rat at 1000 ppm was metastatic in origin and therefore not considered compound related.

Pancreatic effects

An increase in pancreatic nodules was seen at 24 months. Histopathology revealed a significant increase in acinar cell focal hyperplasia (in both sexes) at and above 1000 ppm. Pancreatic weights were not determined at necropsy.

An increased incidence of exocrine pancreatic acinar cell adenomas was seen at all exposure levels except in females at 1000 ppm, however the incidence in females was neither statistically significant or dose related (see Table 6). Sex differences in adenoma incidence were reflected by differences seen in acinar hyperplasia.

Increases in certain malignant tumours (exocrine and endocrine pancreas) were also seen at 24 months but were either metastatic in origin or similar to historical controls and therefore not considered compound related.

Other effects

Animals exposed to 1000 and 5000 ppm exhibited higher survival rates compared to controls. Animal body weights and body weight gain were significantly decreased at 5000 ppm at 12 months and at 1000 ppm in females at 24 months. Decreased kidney weights in both males and females and increased adrenal and lung weights in males were also observed at this exposure level.

Increases in tumours were also seen in other tissues at 24 months but were either not considered biologically significant, were metastatic in origin or exhibited a similar incidence to historical controls and therefore not considered dose related.

Significant biochemical changes (at 24 months) not reported under specific organ effects (above) included increased serum albumin in above 1000 ppm (both sexes) and decreased serum globulin levels above 300 ppm in females and 1000 ppm in males.

Rats exposed to 5000 ppm HCFC-123 showed evidence of CNS effects, that is, less responsive to auditory stimuli compared to controls. Females exposed to 5000 ppm manifested a significant increase in ovarian atrophy and ovarian cysts.

Histological evaluation of the retina indicated a significant increase in diffuse retinal atrophy in both sexes at all exposure levels.

Male and females exposed to 5000 ppm exhibited a 50% decrease in neutrophils at 24 months. Monocytes were decreased to a similar extent in females at 1000 and 5000 ppm.

Table 6 - Summary of tumour incidence in target organs (from chronic inhalation study (Malley, 1992))

Tumour description				*Number of animals with tumours / number examined*							
				Control		*300 ppm*		*1000 ppm*		*5000 ppm*	
Organ	*Tumour*	*Type*	*Origin (organ or cell type)*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Liver	Histiocytic sarcoma	M	Unknown	1/67	0/65	1/66	0/67	5/66	0/67	1/66	0/69
	Hepatocellular adenoma	B	-	3/67	0/65	2/66	5/67*	2/66	2/67	8/66*[1]	7/69*[2]
	Hepatocellular carcinoma	N	-	1/67	0/65	1/66	1/67	0/66	0/67	1/66	1/69
	Lymphosarcoma	M	Unknown	0/67	0/65	1/66	0/67	0/66	0/67	3/66	0/69
	Leukaemia	M	-	0/67	2/65	2/66	1/67	3/66	2/67	1/66	1/69
	Adenocarcinoma	M	Pancreas/prostate	0/67	0/65	0/66	0/67	1/66	1/67	1/66	0/69
	Cholangiofibroma	B	-	0/67	0/65	0/66	0/67	0/66	0/67	0/66	6/69*[2]
	Total hepatic tumours			**5/67**	**2/65**	**7/66**	**7/67**	**11/66**	**5/67**	**15/66**	**15/69**
Exocrine Pancreas	Adenocarcinoma	N	Acinar cell	1/67	0/65	0/66	0/66	0/64	0/67	2/66	0/69
	Adenoma	B	Acinar cell	1/67	0/65	4/66	2/66	12/64*	0/67	14/66*	2/69
	Neurofibrosarcoma	N	-	0/67	0/65	0/66	0/66	1/64	0/67	0/66	0/69
	Histiocytic sarcoma	M	Unknown	0/67	0/65	1/66	1/66	1/64	0/67	0/66	0/69
	Leukaemia	M	-	0/67	1/65	1/66	0/66	2/64	0/67	0/66	0/69
	Lymphosarcoma	M	Unknown	0/67	0/65	0/66	0/66	0/64	0/67	1/66	0/69
Endocrine Pancreas	Adenoma	B	Islet cell	6/67	3/65	5/66	4/66	7/63	3/67	1/66	0/69
	Total pancreatic tumours			**8/67**	**4/65**	**11/66**	**7/66**	**23/64**	**3/67**	**18/66**	**2/69**
Testes	Adenoma	B	Interstitial cell[3] - unilateral	3/67	N/A	6/66	N/A	4/66	N/A	8/66*	N/A
	Adenoma	B	Interstitial cell[3]- bilateral	1/67	N/A	6/66	N/A	5/66	N/A	6/66*	N/A
	Neurofibrosarcoma	M	Unknown	0/67	N/A	0/66	N/A	1/66	N/A	0/66	N/A
	Total testicular tumours			**4/67**	**N/A**	**12/66***	**N/A**	**10/66***	**N/A**	**14/66***	**N/A**

This table comprises tumour incidence data for organs where compound-related tumours were seen at terminal (24 months) sacrifice (includes rats that died in extremis after interim (12 months) sacrifice).

*	*P ≤ 0.05*	*1*	*Includes 3 animals with multiple tumours*	*B*	*Benign*
N/A	*Not applicable*	*2*	*Includes 1 animal with multiple tumours*	*M*	*Malignant (metastatic)*
		3	*Known also as Leydig cell*	*N*	*Malignant (neoplastic)*

10.5 Reproductive toxicity studies

10.5.1 Developmental toxicity studies

Developmental toxicity (inhalation) studies with HCFC-123 have been performed in rats and rabbits.

Two studies have been conducted according to OECD guideline No. 414 in Charles River albino rats. In one study, 25 dams were exposed to 0 or 10,000 ppm of HCFC-123 (Culik & Kelly, 1976). In the other study, 20 dams were exposed to 0 or 5000 ppm (Brewer & Smith, 1977b). In both studies dams were exposed to HCFC-123 by inhalation for 6 h per day during days 6-15 of gestation. Reduced weight gain and CNS depression were observed at 5000 and 10,000 ppm respectively, however there was no evidence of adverse effects on foetal viability, growth or development.

Similarly, there was no evidence of developmental effects in New Zealand white rabbits (24/group) exposed by inhalation to 0, 500, 1500 or 5000 ppm of HCFC-123 for 6 h per day, during days 6-18 of gestation (Schroeder, 1989a). In the range-finding study, (1000, 5000, 10,000 and 20,000 ppm HCFC-123, 6 h per day through gestation days 6-18) increased resorption rate and lower foetal weights were seen at the two highest concentrations, together with foetal tail defects at 20,000 ppm (Schroeder, 1989b). Maternal toxicity, seen as dose-dependent reduced weight gain and inappetence was seen in this study.

10.5.2 Two-generation reproduction toxicity study

A 2-generation inhalation reproduction toxicity study was carried out in Crl: CD (SD) BR VAF/plus rats (Hughes, 1994) in accordance with OECD guideline No. 416. Animals were exposed to 0, 30, 100, 300 or 1000 ppm (0.19, 0.63, 1.88 and 6.26 mg/L) HCFC-123. The F_0 (parental generation) animals, 32 animals/sex/group, were exposed for 6 h per day, 7 days per week from 6 weeks of age for 38 weeks. All animals were exposed during pregnancy, except between day 20 to post-partum day 4.

The F_1 generation (28 pups/sex/group) were derived from the F_0 generation. During the pre-weaning period direct exposure was confined to the lactating (F_0) parent. The F_1 generation were then exposed from 4 weeks of age through to weaning (approximately 28 weeks) of their litters (F_2 generation).

Among F_0 rats, depression in bodyweight gain was seen in males at 100 ppm and above between weeks 14 and 26 only. Bodyweight gain was significantly lower in females at 1000 ppm during the third week of pregnancy (11% lower), but not during lactation. Food intake was decreased in females during lactation at and above 300 ppm. Significant perturbations in circulating cholesterol and triglyceride levels were observed in F_0 rats. Triglycerides (when measured at 38 weeks of age) were depressed at 300 and 1000 ppm (both sexes) and among 100 ppm females. Relative liver weights were significantly increased in all treated F_0 animals. Dose related histological changes were also present at 300 ppm and above, and consisted of enlarged and vacuolated centrilobular and/or periportal hepatocytes in both sexes.

HCFC-123 did not influence pre-mating interval, copulation index or the pregnancy rate of F_0 rats. No significant changes in serum cholecystokinin (CCK) were observed. A decrease in milk fat content was observed at all dose levels, although no dose response relationship was observed. Male hormonal assays (at 14 weeks) revealed significantly increased levels of luteinising hormone (LH) at and above 300 ppm. No treatment related histological abnormalities were seen in the reproductive organs of either sex. There were no significant treatment-related effects on the number of implantation sites, embryonic losses, sex ratio, litter size or the number of live-born pups. Mean pup weights (F_0 offspring) were significantly decreased (around 10%) from day 14 post-partum to weaning at exposures (dose-related) at and above 100 ppm. Sexual maturation was slightly delayed in males at 300 and 1000 ppm.

In the F_1 generation, bodyweight gains were significantly reduced at 300 and 1000 ppm for female and male adults and at 1000 ppm for females during pregnancy (11-20% lower) but not during lactation. Food intake was decreased during lactation in females at 100 (days 4-6), 300 and 1000 ppm. Relative hepatic weights were increased among F_1 weanlings and adults at 300 ppm and 100 ppm respectively. Histological changes, triglyceride and cholesterol perturbations (seen in adults only) were similar to F_0 generation. Significantly reduced relative pituitary and ovarian weights were seen in females at 300 and 1000 ppm respectively, although no treatment-related histological abnormalities were present in the reproductive organs (both sexes - adult F_1 rats). Male hormonal assays revealed significantly decreased levels of progesterone at and above 100 ppm.

HCFC-123 did not influence pre-mating interval, copulation index, pregnancy rate or pup sex ratio of the F_1 generation or effect milk fat content. The number of implantation sites was significantly reduced at 1000 ppm, with a consequent diminution in litter size and litter weights, although foetal survival was not compromised. Mean pup weights in F_1 offspring (F_2 generation) were significantly decreased (around 20%) from day 7 post-partum to weaning at all exposure levels. During this period (from post-partum day 4) direct exposure was confined to the lactating parent.

A sample of male animals drawn from the F_0 (parental) generation was examined in a separate study aimed at investigating the mechanism of the Leydig cell hyperplasia and adenomas found in rats after long-term exposure to HCFC-123 (Sandow et al., 1995b). The sample comprised 4 groups of 18 fertile males exposed for 6 h per day, 7 days a week for 22 weeks to inhalation of 0, 100, 300 or 1000 ppm HCFC-123. Ten males per group were used in an LHRH stimulation test, in which serum levels of LH and testosterone were determined before and after an injection of LHRH. The testes of another 8 males per group were incubated *in vitro* with human chorionic gonadotropin (hCG), which stimulates steroid hormone biosynthesis. The incubation medium and testis tissue were then analysed for content of testosterone, progesterone, oestradiol-17-β, 17α-OH- progesterone and Δ-4-andostenedione.

In the LHRH stimulation test, the rise in serum LH concentrations was impaired after inhalation of HCFC-123 at 300 ppm and 1000 ppm and the response of serum testosterone was slightly diminished in animals exposed to 1000 ppm. The secretory capacity of the testes for testosterone, progesterone, oestradiol-17-β, 17α-OH-progesterone and Δ-4-andostenedione stimulated by incubation with

hCG was not affected by inhalation of HCFC-123 up to 1000 ppm for 22 weeks. The content of these steroid hormones in the testes at the end of incubation was not changed by exposure to HCFC-123, except for a slight reduction of Δ-4-andostenedione at 1000 ppm.

The endocrine effects of HCFC-123 were also investigated in a 14-day study in male and female rats (Hofmann, 1995; Sandow et al., 1995a). This study is reviewed in Section 10.2.

10.5.3 Lactation studies

A lactation study was conducted in pregnant and lactating Sprague-Dawley (Crl:CD BR) rats exposed to 1000 ppm HCFC-123 for 6 h per day from day 5-19 post-conception and again from day 5-21 post-partum (Heinrich, 1996). Within 2 days of birth, litters were crossed over between dams to create 4 groups comprising exposed or control dams rearing litters from different exposed or control mothers. Other dams rearing their natural pups were used for studies of milk production and composition.

Results indicated that HCFC-123 exposure had no effect on pregnancy rate, pregnancy duration, number of implantation sites, number of liveborn pups per dam or weight gain, nor was exposure associated with any abnormal clinical signs or mean pup weight or litter weight at birth, mortality, body weight or gross pathological findings. Dams exposed to HCFC-123 consumed more food than controls on days 10-20 post-conception and less on day 4-21 post-partum. There was a significant increase in absolute and relative liver weights and a significant decrease in serum triglycerides, cholesterol and glucose 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 around 50 µg/mL TFA (the main metabolite of HCFC-123). TFA was also found in the urine of pups reared by dams exposed to HCFC-123. In the pups, there were no significant differences in absolute or relative liver weight, nor were there any abnormal clinical signs or necropsy findings, but pups reared by dams exposed to HCFC-123 showed reduced growth (which was particularly marked in pups of non-exposed mothers) and decreased serum triglycerides. These effects were due to exposure of the lactating dams as there were no effects from exposure during pregnancy.

In another lactation study 2 groups of 4 lactating Rhesus monkeys and their new-born infants were exposed to either air or 1000 ppm HCFC-123 for 6 h per day, 7 days a week for 3 weeks (Slauter, 1997). There were no relevant clinical observations and no differences in body weight or body weight gain between exposed and control mothers or infants. In mothers, exposure to HCFC-123 did not affect serum triglycerides, cholesterol or glucose and did not change the protein or fat content of breast milk. Liver biopsy specimens were taken from the mothers at the end of the study. They revealed exposure-related microscopical lesions including mild to moderate centrilobular hepatocyte vacuolation, trace to moderate centrilobular hepatocyte necrosis and trace to mild subacute inflammation as well as a decrease in microsomal cytochrome-P450 (isoforms 4A1 and 2E1) and peroxisomal β-oxidase activity. As a rule, HCFC-123 was not detected in the blood of mothers or infants, whereas TFA was present in concentrations ranging from 9-70 µg/mL in blood from exposed mothers and from 17-190 µg/mL in blood from their infants. Individual blood levels of TFA

were 2-6 times higher in infants than in their corresponding mothers. Breast milk from exposed mothers contained HCFC-123 and TFA in concentrations ranging from 1-5 µg/mL and 17-30 µg/mL respectively.

10.6 Genotoxicity studies

10.6.1 *In vitro* bioassays

Microbial mutation assays

The mutagenic potential of HCFC-123 has been investigated in *Salmonella typhimurium* (point mutation) and *Saccharomyces cerevisiae* (gene mutation) (Barsky, 1976; Brusick, 1976; Callander, 1989; Longstaff et al., 1984).

In the most recent study (Callander, 1989), HCFC-123 tested (suspension and plate assays) as a vapour and liquid did not induce any significant increases in the observed numbers of revertant colonies in any strain (TA98, TA100, TA1535 TA1537, TA1538) of *Salmonella typhimurium*, either in the presence or absence of an auxiliary metabolising system (S9). The toxic effects observed at the highest exposure level (thinning of background level and/or reductions in colony numbers) confirm that HCFC-123 was tested to an effective maximum dose (750 mg/vessel or 150,000 ppm vapour). Positive controls confirmed that the bacterial strains were responding satisfactorily. The results of this study are in agreement with previous studies carried out by Barsky (1976), Brusick (1976) and Longstaff et al. (1984).

Only one study (Callander, 1989) conformed to OECD guidelines (No. 471) and deficiencies were apparent in earlier studies. In addition, the study in *Saccharomyces cerevisiae* (strain D4) was considered inadequate for assessment due to the fact that no positive controls were included and neither the concentrations of HCFC-123 test doses nor the number of replicates were stated (Brusick, 1976).

Cytogenetic tests

Two cytogenetic tests have been performed using cultured human lymphocytes in which HCFC-123 was tested both in the liquid and gaseous phase (Dance, 1991; Edwards, 1991). Both studies were carried out according to OECD guideline No. 473. The sensitivities of both studies were confirmed by similar clastogenic responses to the positive control substances. The results of these tests are summarised in Table 7.

HCFC-123 elicited a dose-related increase in chromosomal aberrations in human lymphocytes *in vitro* in both studies. Metabolic activation was required to induce a clastogenic response after exposure to HCFC-123 for 3 h (vapour phase assay). After 24 h however, a significant increase in aberrations was seen in both liquid and vapour assays without a metabolising system.

Cell transformation test (Styles assay)

A negative response was reported for HCFC-123 when tested in baby hamster kidney fibroblasts (BHK21 cells) with and without metabolic activation in a Styles assay. No supporting data were provided except that transformation was

Table 7 - Summary of *in vitro* cytogenetic studies

Test system	*Exposure protocol*	*Dose*	*Mean mitotic index*	*Number of cells with aberrations (excluding gaps)*
Human (male) lymphocytes (Dance, 1991)				
300 lymphocytes scored per dose	3-h exposure (without S9)	0% v/v	25.2	1
		0.005% v/v (73 µg/mL)	19.6	2
		0.01% v/v (146 µg/mL)	21.7	3
		0.02% v/v (292 µg/mL)	21.1	3
		CBC (2µg/mL)	14	91
HCFC-123 (liquid phase)	3-h exposure (with S9)	0% v/v	23.8	1
		0.01% v/v (146 µg/mL)	21.8	2
		0.02% v/v (292 µg/mL)	14.7	6
		0.04% v/v (584 µg/mL)	6.6	5
		CP (6 µg/mL)	8.4	106
	24-h exposure (without S9)	0% v/v	30.7	2
		0.0025% v/v (36 µg/mL)	27.4	3
		0.005% v/v (73 µg/mL)	21.5	10*
		0.02% v/v (292 µg/mL)	9.7	31†
		CBC (2µg/mL)	22.9	70
Human (male) lymphocytes (Edwards, 1991)				
300 lymphocytes scored per dose	3-h exposure (without S9)	0% v/v	24.9	1
		7.5% v/v (75,000 ppm)	23.9	3
		15% v/v (150,000 ppm)	17.9	0‡
		30% v/v (300,000 ppm)	10.3	5‡
		CBC (2µg/mL)	18.5	60
HCFC-123 (vapour phase)	3-h exposure (with S9)	0% v/v	22.2	4
		7.5% v/v (75,000 ppm)	24.1	3
		15% v/v (150,000 ppm)	21.0	4
		30% v/v (300,000 ppm)	9.5	23‡§
		CP (6 µg/mL)	15.2	107
	24-h exposure (without S9)	0% v/v	16.6	1
		2.5% v/v (25,000 ppm)	19.1	9†
		5% v/v (50,000 ppm)	13.2	18§
		10% v/v (100,000 ppm)	5.9	24§
		CBC(2µg/mL)	13.5	118

* *0.05>P>0.01*
† *0.01>P>0.001*
‡ *Increase in number of polyploid cells*
§ *P<0.001*
CP Cyclophosphamide (positive control)
CBC Chlorambucil (positive control)
S9 Exogenous metabolic activation system

determined by the observation of sustained cell growth (in semisolid agar) and that the criterion for a positive result was a transformation frequency in excess of 5 times the spontaneous rate. The sensitivity of the study was confirmed by appropriate positive control substances (Longstaff et al., 1984).

10.6.2 *In vivo* bioassays

Cytogenetic test

HCFC-123 has also been tested *in vivo* for its ability to induce chromosomal aberrations in peripheral lymphocytes in rats (Marshal, 1991). In this study, rats (10 males per dose level) were exposed by inhalation to HCFC-123, in the dose range of 300 to 5000 ppm, for 6 h per day, 5 days per week for 14 weeks. There

was no evidence of HCFC-123 induced clastogenicity in the peripheral lymphocytes at 5000 ppm. Several deficiencies in experimental design (such as no analysis of lymphocytes at lower exposure levels and a lack of cell toxicity at the upper dose tested) were noted in this study. An increase in the number of cells with aberrations was observed for the positive control cyclophosphamide (20 mg/kg given by intraperitoneal injection).

Micronucleus test (bone marrow)

Groups of NMRI mice (5 animals per sex per group) were exposed, nose-only, to 2,000 ppm, 6,000 ppm and 18,000 ppm HCFC-123 for 6 h (Muller & Hofmann, 1988). The incidence of micronucleated polychromatic or normochromatic erythrocytes in each treatment group was within the normal range of the negative control. Similarly the ratio of polychromatic to normochromatic erythrocytes in both male and female animals did not differ from control values. The sensitivity of the test was confirmed by a statistically significant increase in the number of micronucleated polychromatic erythrocytes in the positive control group.

Unscheduled DNA synthesis

HCFC-123 was tested for DNA damaging effects in rat hepatocytes, in two independent experiments, following inhalation exposure to 12,500 ppm and 20,000 ppm for 6 h (Kennelly, 1993). In both experiments, 5 male rats per group were used and 60 hepatocytes were scored per animal. Based on the evaluation of both the mean net nuclear grain count and percentage of cells in repair, HCFC-123 did not cause unscheduled DNA synthesis (UDS) in rat liver *in vivo*. The sensitivity of the test system was validated by an induction of UDS in the positive control group receiving N-nitrosodimethylamine and non-significant UDS in the negative control group. Results were consistent for both experiments.

10.7 Summary of toxicological data

Table 8 summarises results of all assessed studies, including critical effects together with NOAELs or LOAELs (where determined).

Table 8 - Summary of toxicological data

Type of study	*Route of administration*	*Animal/ test system*	*Result(s) (critical effect/toxicological endpoint)*	*Section*
Acute toxicity				
Lethality				
	Oral	Rat (m)	ALD = 9000 mg/kg b.w.	10.1.1
	Dermal	Rat	LD_{50} > 2000 mg/kg b.w.	10.1.2
		Rabbit		
	Inhalation	Rat (m)	LC_{50} (4hr) = 32,000 - 53,000 ppm	10.1.3
		Mouse	LC_{50} (30 min) = 74,000 ppm	10.1.3
		Hamster (m)	LC_{50} (4hr) = 28,400 ppm	10.1.3
Liver effects	Inhalation	Guinea pig	Hepatotoxic at lowest test dose (1000 ppm)	10.1.3
Behaviour	Inhalation	Rat (m)	EC_{50} (1hr) = 4000 ppm No effects at 2,500 ppm	10.1.3
Cardiac sensitisation	Inhalation	Dog (m)	EC_{50} (5 min) = 19,000 ppm No effects at 10,300 ppm	10.1.3
Irritation				
	Skin	Rabbit	Non irritant	10.2.1
		Guinea pig (m)	Non irritant	
	Eye	Rabbit	Slight irritant	10.2.2
Sensitisation				
	Skin	Guinea pig	Negative	10.3
Repeated dose toxicity				
Subacute	Inhalation	Rat	CNS depression (NOAEL = 1000 ppm) Hepatic effects (LOAEL = 1000 ppm) Testicular effects (NOAEL = 10,000 ppm)	10.4.1
		Guinea pig (m)	CNS depression Hepatic toxicity	10.4.1
Subchronic	Inhalation	Rat	CNS depression (LOAEL = 1000 ppm) Hepatic effects (LOAEL = 300 ppm; NOAEL[1] = 100 ppm)	10.4.2 10.5.2
		Dog	CNS depression (NOAEL = 1000 ppm) Hepatic effects (NOAEL = 1000 ppm)	10.4.2
Neurotoxicity	Inhalation	Rat	No effects observed	10.4.2
Carcinogenicity	Inhalation	Rat	CNS depression (NOAEL = 1000 ppm) Benign tumours (LOAEL = 300 ppm) Non-neoplastic effects[2] (LOAEL = 300 ppm)	10.4.3
Reproductive effects				
Development	Inhalation	Rat	No adverse developmental effects	10.5.1
		Rabbit	Effects only at maternally toxic doses	
Fertility	Inhalation	Rat	Effects only at maternally toxic doses	10.5.2
Lactation	Inhalation	Rat	Reduced pup growth (LOAEL[3] = 30 ppm)	10.5.3
		Monkey	No effects observed in breast-fed infants	10.5.3
Genotoxicity *(in vitro)*				
Mutation		*S. typhimurium*	Negative	10.6.1
		S. cerevisiae	Inadequate study	10.6.1
Chromosomal aberration		Human lymphocytes	Positive	10.6.1
Cell transformation		BHK21 cells	Negative	10.6.1
Genotoxicity *(in vivo)*				
Chromosomal aberration		Rat lymphocytes	Negative	10.6.2
Micronucleus induction		Mice	Negative	10.6.2
UDS		Rat	Negative	10.6.2

1. *Determined (at 28 weeks) in 2-generation m reproductive toxicity study*

Males only (male and female animals used unless stated)

2. *Histopathological effects in liver, pancreas and t estes*

3. Determined in 2-generation reproductive toxicity study

ALD	*Approximate lethal dose*
LOAEL	*Lowest observed adverse effect level*
NOAEL	*No observed adverse effect level*
UDS	*Unscheduled DNA synthesis*

11. Human Health Effects

The available data on human health effects of HCFC-123 are limited to a single report of effects following acute exposure (Carrier, 1993) and three reports of effects following repeated exposure to the chemical (Allied, 1998a; Hoet et al., 1997; Takebayashi et al., 1998a). However, health effects from exposure to structural analogues (including other HCFCs, CFCs and halons) are well documented. As HCFCs show similar toxicological profiles to CFCs and halons in animals (IPCS, 1990; IPCS, 1992), similarities might also be expected in humans. Thus a consideration of effects produced by CFCs and halons in humans is considered relevant to complete the assessment of potential human health hazards from exposure to HCFC-123.

11.1 Acute effects

11.1.1 HCFC-123

Effects such as dizziness, headaches and nausea were reported in around 40 workers exposed to HCFC-123 following the rupture of an industrial chiller (Carrier, 1993).

11.1.2 CFCs, halons and other HCFCs

In humans acute health effects from exposure to CFCs, halons and other HCFCs include CNS effects, cardiopulmonary effects, hepatic effects and asphyxiation.

Bronchospasm, bradycardia and T-wave inversion have been reported in human studies with bronchodilator and commercial aerosols containing CFC-11 and CFC-12. Exposure of chiller maintenance technicians to 10,000 ppm (50 g/m^3) CFC-12 for 2 h led to a reduction in ventilatory lung capacity and a significant decrease in heart rate (IPCS, 1990). Similar effects were seen in volunteers exposed to 27,000 ppm CFC-12 for up to 1 min (Aviado & Micozzi, 1981). Volunteers exposed to 4500 ppm CFC-113 for up to 2 h suffered significant impairment of manual dexterity and concentration (Procter et al., 1989). NIOSH reported the deaths of 12 workers due to asphyxiation or cardiac arrhythmia resulting from excessive exposure[1] to CFC-113 used as a solvent (IPCS, 1990). Another occupational death was reported (IPCS, 1990) from exposure to CFC-113 vapour at a concentration of around 1000 g/m^3 (130,000 ppm). Fatalities have been reported from the use and abuse of aerosol products containing CFC propellants (Aviado & Micozzi, 1981; Zakhari & Aviado, 1982).

Effects reported from exposure to bromofluorocarbon (halon) fire extinguishants include paraesthesia, tinnitus, anxiety, slurred speech, electroencephalographic changes and eye and respiratory irritation (Aviado & Micozzi, 1981). Convulsive seizures and respiratory arrest have been documented in firefighters exposed to chlorobromomethane (Procter et al., 1989). Human volunteers exposed to Halon

[1] Data not provided.

1301 showed electrocardiographic irregularities at exposures from 70,000 to 150,000 ppm with paraesthesia and other CNS effects above 100,000 ppm (Procter et al., 1989). Fatalities have been reported for Halon 1211 (Lerman et al., 1991), including a death from exposure to an estimated concentration of around 120,000 ppm Halon 1211 resulting from discharge (around 3 kg) of extinguishant into a confined space (7,000 L chamber).

Leakage of HCFC-22 refrigerant at a skating rink resulted in the death of one person and 34 cases of acute intoxication that included nausea, CNS depression, cough, etc. (Checket-Hanks, 1991).

Halothane (HCFC-123b1) toxicity has been well documented in humans. Exposure levels of 10,000-40,000 ppm (1-4%) during anaesthesia has been associated with cardiac effects and toxic hepatitis (known as 'halothane hepatitis'), both of which have resulted in fatalities, although extremely rare with halothane hepatitis (Atkinson et al., 1977; Ray & Drummond, 1991). Halothane hepatitis may be an immune-mediated disease and the fact that halothane and HCFC-123 exhibit similar patterns of trifluoroacetylated liver proteins (Harris et al., 1991) and serum antibodies (Martin, 1993) (in animal studies) has led to concern over HCFC-123 being capable of eliciting a similar hepatic response in humans (Hubbard et al., 1991; Martin, 1993). It has also been suggested that a potential may exist for cross-sensitisation between HCFC-123 and structurally analogous anaesthetic agents (Martin, 1993). Hepatic toxicity has been well documented in humans from exposure to other halogenated alkanes, including methyl chloride, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane and mono- and di-bromoethane (Procter et al., 1989).

11.2 Dermal effects

Some fluorocarbon liquids remove oils from the dermis, causing irritation and development of dry, sensitive skin, particularly after repeated contact (Aviado & Micozzi, 1981).

Limited evidence of skin sensitisation exists for both CFC-11 and CFC-12 from use in deodorant sprays (IPCS, 1990).

11.3 Effects from repeated exposure

Liver effects

Three reports of liver effects (comprising 26 cases) in workers exposed to HCFC-123 were provided for assessment.

Hoet et al. (1997) reported 9 cases of liver disease in gantry drivers at a smelting depot in Belgium. The cases occurred 1-4 months after the refrigerant utilised in the crane cabin air-conditioning system had been replaced by a blend containing 57% HCFC-123, 40% HCFC-124 and 3% propane (Verlinden, 1997). One driver was admitted to hospital. Blood biochemistry showed increased levels of AST, ALT, ALP, GGT and total and conjugated bilirubin and decreased prothrombin activity. Autoimmune, viral and drug- or alcohol-induced hepatitis was ruled out. A liver biopsy specimen showed focal liver cell necrosis and plugging of the bile ducts. Trifluoroacetylated liver proteins were identified by an immunochemical method. The symptoms regressed during the period of non-exposure, but recurred

when the driver returned to work two months later. Eight other drivers showed signs of varying degrees of liver abnormalities. Serum antibodies to at least one of two human liver enzymes (cytochrome-P450 isoform 2E1 and protein disulphide isomerase isoform P58) were detected in 5 of 6 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. Exposure levels were not reported by Hoet et al. (1997). However, an air sample collected from the crane cabin before the air-conditioning system was repaired was found to contain 50- 150 mg/m^3 of total HCFCs (Verlinden, 1997).

Another 8 cases were reported in workers exposed to the vapours of solvent degreasers containing either 97.5% HCFC-123, 2.3% methanol and 0.2% nitromethane or 100% HCFC-123 (Allied, 1998a). Two months after a US factory converted to using HCFC-123 in their degreaser, two employees who worked closely with the solvent and the degreaser were found to have liver disease, with high blood levels of liver enzymes, high total and conjugated bilirubin and negative tests for viral hepatitis. Subsequent testing of all 27 factory employees revealed 4 additional cases of elevated liver enzymes in employees who did some, little or no work with the degreaser. When retested one month later, 5 of the 6 affected employees had improved significantly, whereas one had deteriorated and there was one new case with slightly elevated AST and ALT levels (Table 9). 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. As shown in Table 10, air monitoring was conducted over 2 days when the factory converted to using the HCFC-123 solvent and again after the initial cases of liver disease had been diagnosed. Although air sampling was not concurrent with blood test dates, the data collected indicate that there were low but measurable levels of HCFC-123 (5-12 ppm) throughout the factory and the potential for high short- term exposures to HCFC-123 in areas where the degreaser was used or maintained, with concentrations varying between 7 and 460 ppm (Table 10). There was also one case of elevated liver enzymes (AST, ALT and GGT) and negative tests for viral hepatitis in a technician employed in the manufacturer's research laboratory where HCFC-123 was tested and evaluated. Air levels in the laboratory area were generally below 50 ppm HCFC-123.

Table 9 – Clinical chemistry findings in workers exposed to HCFC-123 solvent vapours (Allied, 1998a)

Worker No.	Work with solvent	Date*	Test (upper limit of normal range)†						
			AST (42)	ALT (48)	GGT (45)**	LDH (250)	ALP (125)	TBIL (1.3)	CBIL (0.4)
5	Yes	26/04/96	19	16	-	-	-	-	-
		10/10/97	1370	2675	-	-	-	-	-
		21/10/97	1100	1445	-	-	-	-	-
		07/11/97	887	1327	569	441	155	1.5	0.9
		09/12/97	147	268	236	166	74	0.9	0.0
26	Yes	07/10/97	584	1559	-	-	-	-	-
		20/10/97	129	550	-	-	-	-	-
		05/11/97	75	200	-	-	-	-	-
		07/11/97	69	141	54	227	95	2.0	0.7
		09/12/97	37	60	30	151	59	3.2	0.0
18	Some	07/11/97	201	562	354	275	95	0.3	0.0
		09/12/97	30	90	136	144	76	0.4	0.0
15	Little or none	07/11/97	190	362	54	176	52	0.5	0.2
		09/12/97	207	554	75	130	50	0.5	-
6	Little or none	07/11/97	113	162	154	332	114	0.5	0.0
		09/12/97	30	52	79	178	88	0.4	0.0
16	Little or none	07/11/97	46	59	56	205	95	0.9	0.0
		09/12/97	24	35	34	120	73	0.6	0.0
9	Little or none	07/11/97	25	14	21	186	57	1.1	0.0
		09/12/97	53	96	24	146	50	0.8	0.0

*	*The factory was converted to using HCFC-123 solvent on 19/08/1997*	*GGT*	*γ-Glutamyl transferase*
†	*Enzymes in U/L, bulirubin in mg/dL*	*LDH*	*Lactate dehydrogenase*
**	*Upper limit in males is 65 (Allied, 1998b)*	*ALP*	*Alkaline phosphatase*
AST	*Aspartate transaminase*	*TBIL*	*Total bilirubin*
ALT	*Alanine transaminase*	*CBIL*	*Conjugated bilirubin*

Table 10 – Exposure levels in factory using HCFC-123 solvent (Allied, 1998a)

*Date**	*Monitoring*	*Description*	*Duration (min)*	*Result (ppm)*
19/08/97	Personal	Charging, degreaser	21	460
	Personal	Working, degreaser	122	110
20/08/97	Personal	Working, degreaser	375	24
	Personal	Unloading, degreaser	21	160
16/10/97	Personal	Working, degreaser	183	6.5
17/10/97	Personal	Working, degreaser	146	8.8
	Personal	Working, desk	124	9.8
	Area	Basket	117	9.1
	Area	Desk	105	9.1
12/11/97	Personal	Plant-wide	~ 330	5.3-12.0

* *The factory was converted to using HCFC-123 solvent on 19/08/97*

Additional cases of liver disease occurred in a factory in Japan set up to manufacture miniature heat-exchangers for industrial use (Takebayashi et al., 1998a; Takebayashi, 1999). The outbreak involved 9 out of 14 workers who filled the containers with HCFC-123, sealed them and checked them for leakage. Four to 5 weeks after production commenced, 4 workers showed sign of general malaise, poor appetite and abdominal pain and elevated levels of AST, ALT, ALP, GGT and LDH. Two of them had elevated levels of total and conjugated bilirubin and were clinically jaundiced. When tested for hepatitis B antigen and hepatitis A and C antibodies, one of the 4 workers was positive for hepatitis A antibodies. Five other workers who generally did not work full-time with HCFC- 123 had slight increases in AST and ALT but no symptoms apart from occasional abdominal pain and headache. A workplace inspection revealed that the heat- exchangers were filled with HCFC-123 in a room which was not ventilated and identified the chemical as the only hazard in the workplace. Exposure levels were not measured at the time. In a subsequent simulation of the original working conditions, air levels of HCFC-123 ranged from 24 to 1125 ppm with a geometric mean of 225 ppm at the site where the containers were filled with the chemical and from 4-41 ppm with a geometric mean of approximately 20 ppm in adjacent areas (Takebayashi et al., 1998b). All workers recovered in 6 weeks and no new cases occurred after an exhaust system was installed that maintains air levels at about 1 ppm HCFC-123 (Takebayashi, 1999).

Other effects

There are no reports available of other human health effects following prolonged or repeated exposure to HCFC-123. However, exposure to other CFCs or HCFCs has been associated with neurological disorders, haematological effects, coronary heart disease and reproductive effects.

No electrocardiogram or pulmonary function effects were seen in human volunteers exposed to 250-1000 ppm CFC-11 or CFC-12 (venous blood levels of up to 4.7 mg/L) for 8 h per day for up to 4 weeks (IPCS, 1990).

Approximately 200 workers (male and female) reportedly exposed to HCFC-22, CFC-113 and HCFC-142b (in addition to other identified CFCs) were studied by Filicheva (1975). Neurological disorders, including neurovegetative system

disturbances and polyneuritis of the upper extremities, were reported in approximately 70% of workers. Reduced erythrocyte haemoglobin levels and sedimentation rate in addition to moderate leucocytosis were also reported. Exposure profiles were not reported in this study. In another study 50 workers exposed to 45-4700 ppm CFC-113 for around 2.5 years showed no signs or symptoms of adverse effects (Aviado & Micozzi, 1981).

Hospital personnel exposed to HCFC-22 during preparation of frozen tissue sections exhibited a higher (3.5-fold excess) incidence of coronary heart disease (Aviado & Micozzi, 1989), although an epidemiological study in workers exposed to HCFC-22 (amongst other CFCs) showed no excess mortality from cardiovascular or malignant disease (Procter et al., 1989).

Although epidemiological studies have reported associations between exposure to anaesthetic vapours (including halothane) and the occurrence of cancers, spontaneous abortions and congenital abnormalities in female hospital personnel, the evidence is considered inadequate (Aviado & Micozzi, 1989; IARC, 1987).

11.4 Toxic combustion products

Pyrolysis of CFCs and HCFCs (including HCFC-123) can lead to the formation of a number of toxic products including free halogens, HCl and HF and phosgene (carbonyl chloride). Cases of phosgene poisoning have been reported following thermal decomposition of CFC-11 propellant (Aviado & Micozzi, 1989). Signs and symptoms of Cl_2, F_2, HCl, HF and phosgene poisoning include eye and respiratory irritation, vomiting, dyspnoea and cyanosis. Acute exposure to 50 ppm phosgene, 50-250 ppm F_2, HCl or HF and 1000 ppm Cl_2 may be fatal (Procter et al., 1989). Isopropenyl-1-methylcyclohexene is added to extinguishant blends containing HCFC-123 to reduce the quantity of certain pyrolysis products. With respect to HCFC-blend fire extinguishants, toxic products may also arise from the reaction of thermal decomposition products with the material on fire.

12. Human Health Hazard Assessment and Classification

This Section integrates data on kinetics and metabolism, animal toxicity and human effects in order to characterise potential human health hazards from exposure to HCFC-123 and classify these hazards. The classification criteria used throughout are the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1998).

Where adequate human data are not available, information from experimental studies (animal and *in vitro* bioassays) form the basis for assessment. In extrapolating results from experimental studies to humans, consideration has been given to relevant issues such as quality of data, weight of evidence, metabolic and mechanistic profiles and relevance of exposure levels.

12.1 Toxicokinetics and metabolism

In vivo studies indicate that HCFC-123 is metabolised similarly in rats and guinea pigs in terms of uptake (absorption via inhalation), tissue distribution and extent and rate of elimination of metabolites in urine.

Partition coefficients for HCFC-123 in various tissues indicate that absorption is expected to occur readily. HCFC-123 is taken up mainly by the liver, kidney and testes in rats and guinea pigs.

In vitro studies indicate that HCFC-123 is metabolised by the same cytochrome P-450 isoenzyme (CYP 2E1) in both animal and human microsomal preparations. In both systems the main metabolites are TFA and chlorodifluoroacetic acid.

Biotransformation studies indicate that the major HCFC-123 metabolite *in vivo* is TFA. Approximately 25% of the administered dose is recovered in rat and guinea pig urine. TFA is excreted in the milk of lactating rats and monkeys. Data suggest that cytochrome P-450 mediated biotransformation of HCFC-123 to TFA is suppressed above 1000 ppm in rats because of substrate inhibition.

Evidence indicates that reactive metabolites are associated with acute hepatotoxicity. Liver protein adducts (increased by phenobarbitone pretreatment and by glutathione depletion) are formed with HCFC-123 in rats and guinea pigs. Although distribution to other tissues occurs, no evidence of covalent binding was seen in testes or pancreas (both target organs for toxicity from repeated dose studies with HCFC-123).

The available evidence indicates that HCFC-123 is metabolised similarly in rats and guinea pigs. Furthermore *in vitro* evidence indicates that metabolism is likely to be similar in humans. The increased rate (>10-fold) of biotransformation of HCFC-123 to TFA seen in human liver cell preparations (compared to rat liver cell preparations) indicates that quantitative differences in oxidative metabolism and elimination may exist *in vivo* between humans and rodents with resultant differences in toxicity profiles and species sensitivity.

12.1.1 Comparative metabolism with halothane

A number of similarities exist between HCFC-123 and halothane metabolism. Halothane toxicity and metabolism has been extensively investigated due to its use as an anaesthetic agent in humans. Metabolic comparisons between the two substances are therefore valid with respect to providing an insight into potential mechanisms of toxicity for HCFC-123 and relevance to humans. Of the information provided for assessment HCFC-123 and halothane elicited similar acute hepatotoxic profiles in guinea pigs and similar propensities for peroxisome proliferation in rats. Only HCFC-123 has been shown to induce tumours in animal bioassays. Halothane did not induce tumours in inhalation studies in rats and mice (IARC, 1987). Mice were exposed *in utero* and then three times weekly for 78 weeks at the maximum tolerated dose, or 24 times at several dose levels. The rats were exposed to a low level of halothane alone or in combination with nitrous oxide.

HCFC-123 and halothane exhibit similar biotransformation profiles, undergoing both oxidative and reductive metabolism. Both substances undergo oxidative metabolism to trifluoroacetyl chloride (the putative metabolite associated with protein binding) and TFA (the putative metabolite associated with peroxisome proliferation) in addition to reductive metabolism (minor pathway) to HCFC-133a and 2-chloro-1,1-difluoroethene (CDE). There is evidence to suggest that with HCFC-123 this metabolic pathway only occurs under conditions of reduced oxygen, and hence under normal conditions of use this pathway is likely to be more relevant to halothane than to HCFC-123 metabolism.

At high levels HCFC-123 is metabolised (Harris et al., 1992; Vinegar et al., 1994) (in rats) to TFA to a greater extent (approximately 50%) than halothane, despite the fact that HCFC-123 is less lipophilic than halothane (Loizou et al., 1994) and hence is not expected to be so readily absorbed. These results were confirmed *in vitro* (Urban et al., 1994). Both halothane and HCFC-123 are reported to suppress their own metabolism to TFA at around 1000 ppm (Vinegar et al., 1994).

Protein binding profiles are very similar for HCFC-123 and halothane with a similar degree of trifluoroacetylated liver protein adducts at equivalent exposure levels (Harris et al., 1992; Marit et al., 1994). In addition, liver samples from HCFC-123 and halothane exposed guinea pigs exhibited similar cross reactivity to anti-trifluoroacetyl antibodies (Marit et al., 1994). In rats exposed to halothane, several trifluoroacetylated proteins have been isolated from liver microsomes and identified (Cohen et al., 1997). These proteins are associated with the endoplasmic reticulum of hepatocytes and many are involved in the maturation of newly synthesised proteins. Trifluoroacetylation may interfere with their functions and/or alter their antigenicity.

Despite the lower lipophilicity of HCFC-123 compared to halothane, available studies indicate that the amount of hepatic protein binding and TFA formation are similar for both compounds. In summary, the similarities between HCFC-123 and halothane in chemical structure, metabolism (including protein binding) and acute toxicity in animal studies (Marit et al., 1994; Keller, 1998), indicate a potential for similarities in toxicity profiles in humans. This is supported by the finding in workers accidentally exposed to HCFC-123 of trifluoroacetylated liver proteins and serum antibodies to human liver enzymes, both of which are common in halothane hepatitis in humans (Hoet et al., 1997).

12.2 Toxicity of HCFC-123 impurities

Toxic impurities are found in commercial grade HCFC-123.

1,2-dichloro-1,1,2-trifluoroethane (HCFC-123a) has been identified as the major impurity in HCFC-123 and is usually present in concentrations of less than 5% v/v (up to 13% v/v has been reported - see PEC4, Section 4). Studies in rats indicate similar toxicity profiles for HCFC-123a and HCFC-123 with respect to liver damage and hepatic peroxisome proliferation (Warheit, 1993). Although in this study HCFC-123a, but not HCFC-123, elicited minor pancreatic effects (acinar cell inflammation and degeneration), this was not considered significant, particularly as similar pancreatic effects were associated with TFA, the major metabolite of HCFC-123. Therefore, it is unlikely that HCFC-123a *per se* is primarily responsible for any of the critical effects seen from repeated exposure to HCFC-123, but probably contributes (additive effect) to the overall toxicity profile of HCFC-123.

In addition to HCFC-123a, other halogenated hydrocarbon impurities found in HCFC-123 (listed in PEC4, Section 4, Table 1) amount to a total of around 0.5% v/v. Saturated hydrocarbons comprise most of these impurities, with 1,1,2-trichlorotrifluoroethane (CFC-113) being the most ubiquitous, present at levels up to 0.2%. The maximum concentration of unsaturated hydrocarbon impurities in HCFC-123 is estimated to be around 0.02%. At such low concentrations it is considered unlikely that either saturated or unsaturated hydrocarbon impurities contribute to the toxicity profile of HCFC-123.

12.3 Health effects evaluation

12.3.1 Acute effects

No data exist on the oral and dermal toxicity of HCFC-123 in humans. Studies in animals show that HCFC-123 has low acute oral toxicity (ALD of approximately 9000 mg/kg in rats) and low dermal toxicity (LD_{50} > 2000 mg/kg in rats and rabbits). In rats and hamsters, the acute inhalation LC_{50} (4 h) for HCFC-123 is low, 28,000-53,000 ppm (175-330 mg/L).

In a single acute inhalation study carried out in guinea pigs, hepatotoxicity was seen at the lowest test level of 1000 ppm (6.25 mg/L) HCFC-123. Similar lesions were described in the same study with the HCFC-123 analogue, halothane. Such lesions were reported as reversible (by 1 week post-exposure) in other studies on halothane exposed guinea pigs (Lunam et al., 1985). Halothane is associated with both fatal (rare) and non-fatal hepatitis in humans. Similarities in metabolism, immunotoxicology and hepatic lesions between halothane and HCFC-123 in rats and guinea pigs support the possibility that acute exposure to high levels of HCFC-123 may elicit a similar toxicological profile to halothane in humans.

Acute reversible CNS effects have been reported in humans and animals following inhalation of HCFC-123. Exposure levels were not categorised in cases of human poisoning. No CNS effects were seen at 2500 ppm (15.6 mg/L) HCFC-123 in a behavioural study in rats.

CFCs and HCFCs are known to sensitise the heart to adrenaline-induced arrhytmias (Zakhari & Aviado, 1982). HCFC-123 caused cardiac sensitisation in dogs exposed to levels around 20,000 ppm (125 mg/L), whereas no effects were seen at 10,000 ppm (62.5 mg/L) (Trochimowicz & Mullin, 1973). Exposure of dogs to an atmosphere of 12% or 14% NAF S-III (a blend of HCFC-22, HCFC-124 and HCFC-123) showed an increased cardiac sensitivity to adrenaline at both dose levels and resulted in the death of 1 animal exposed to a concentration of 14% (Banks, 1997). Although no data were available on cardiac sensitisation effects for HCFC-123 in humans, such effects have been documented following exposure to other CFCs, including CFC-12, where sensitisation was reported at 10,000 ppm (IPCS, 1990).

In humans, liver toxicity, cardiac sensitisation and CNS depression are likely to be the critical effects following acute exposure to HCFC-123, although asphyxiation may also occur at very high levels.

Classification status

HCFC-123 does not meet the Approved Criteria (NOHSC, 1998) for acute lethal effects or for non-lethal irreversible effects after a single exposure by oral, dermal or inhalation exposure.

12.3.2 Irritant effects

Dermatological problems have been reported in humans exposed to other fluorocarbons (Aviado & Micozzi, 1981). However, no reports were available on the skin or eye irritation potential of HCFC-123 in humans.

Tests in rabbits and guinea pigs indicate that HCFC-123 is not a skin irritant (Brock, 1988c; Goodman, 1975). HCFC-123 was a slight eye irritant in rabbits (Britelli, 1975).

Classification status

HCFC-123 does not meet the Approved Criteria (NOHSC, 1998) for irritant effects (skin and eyes).

12.3.3 Sensitising effects

No data exist on the skin or respiratory sensitisation potential of HCFC-123 in humans, although there is limited evidence of skin sensitisation for CFC-11 and CFC-12 used in deodorant sprays (IPCS, 1990). A study on skin sensitisation of HCFC-123, carried out in guinea pigs (Goodman, 1975), was considered negative under the conditions of the study. It is possible that the doses used may not have been sufficiently high to elicit a sensitisation response. However, sensitisation has not been reported in other structural analogues of HCFC-123 (IPCS, 1990; IPCS, 1992). No studies were available on the sensitisation potential of HCFC-123 in animals by inhalation.

Classification status

HCFC-123 does not meet the Approved Criteria (NOHSC, 1998) for sensitising effects (skin).

12.3.4 Effects (other than carcinogenic and reproductive) from repeated exposure

There are reports of a total of 26 cases of liver effects in humans following repeated exposure to HCFC-123. In humans, repeated exposure to other CFCs and HCFCs has also been associated with haematological effects, neurological disorders and cardiac effects.

Neurological effects

Although behavioural effects and CNS effects have been seen in animals repeatedly exposed to HCFC-123, histological examination in rats of brain, spinal cord and nerve fibres indicates no neurotoxicity at the highest exposure (inhalation) level of 5000 ppm (Coombs, 1994).

A NOAEL for CNS (anaesthetic) effects of HCFC-123 in rats and dogs was determined at 1000 ppm (6.25 mg/L) from chronic and subchronic studies.

Liver effects

A total of 26 cases of liver effects have been reported in humans exposed to HCFC-123 (Allied, 1998a; Hoet et al., 1997; Takebayashi et al., 1998a)[1]. The damage reported was limited to increased liver enzymes and, in severe cases, reduced prothrombin activity and/or increased levels of total and conjugated bilirubin. A liver biopsy specimen obtained from one of the cases described by Hoet et al. (1997) showed focal liver cell necrosis and cholestasis. All workers on whom follow-up tests were performed improved or normalised when exposure was reduced or terminated.

In 2 of the 3 incidents the actual exposure level was not reported or measured, although other information indicates that it probably was in the range of 5-1125 ppm. One report concerned 7 workers exposed to HCFC-123 vapours at air levels ranging from 5-500 ppm and one laboratory technician exposed to levels that were generally less than 50 ppm (Allied, 1998a-b). Air monitoring was conducted when the factory first converted to using HCFC-123 and again about 7 weeks later just after the intial cases of liver dysfunction had been discovered. Monitoring was repeated several times over the next two months until HCFC-123 use was discontinued and consistently showed 6-8-h TWA levels in the 5-12 ppm range throughout the factory. Although most workers with liver function abnormalities improved during this period, one worker had worsening of already abnormal AST and ALT levels and another employee developed slightly elevated levels of AST and ALT. Based on the air level measurements reported above and in Table 10 and a number of assumptions including use volume, air flow in the facility, shipment quantities etc., the manufacturer concluded that the exposure limit for HCFC-123 should be lower than 5-12 ppm to protect most individuals from acquiring liver function abnormalities (Allied, 1998b).

Human liver toxicity has been well documented for structural analogues of HCFC-123, including halothane, which has a similar metabolic, immunological

[1] Nine cases were also exposed to HCFC-124. However, whereas in subchronic toxicity studies in rats HCFC-123 causes liver injury at and above 300 ppm, there were minimal liver abnormalities in animals exposed to 50,000 ppm HCFC-124 and none at all in animals exposed to 15,000 ppm HCFC-124 (Malley et al., 1996).

and hepatotoxic profile to HCFC-123 in animal studies (Procter et al., 1989; Ray & Drummond, 1991).

Adverse hepatic effects were seen in rats, guinea pigs, dogs and monkeys following repeated exposure (inhalation) to HCFC-123. The types of lesions observed varied between species and with duration of study. Generally, the lesions observed were hepatocyte enlargement and vacuolation (at 300 ppm) with necrosis and fatty change (at and above 1000 ppm). Such lesions were reported as reversible (30 days post-exposure) in a single 90-day study in rats exposed to 500-5000 ppm HCFC-123 and were not significantly increased at 300 ppm after 12 months in the 2-year inhalation study. The NOAEL reported for hepatic effects in rats (28 weeks exposure in a 2-generation reproductive toxicity study) was 100 ppm (0.63 mg/L).

Testicular effects

Adverse testicular effects were seen in subacute inhalation studies in rats (NOAEL = 10,000 ppm) but not in guinea pigs. The LOAEL determined from chronic exposure (inhalation) in rats is 300 ppm (1.9 mg/L).

Pancreatic effects

A statistically significant decrease in insulin levels was seen in a subacute study in rats exposed to approximately 18,000 ppm HCFC-123. This finding was considered to be a physiological response to decreased glucose levels rather than an indicator of diminished pancreatic function (Warheit, 1993), a finding supported by data from a 90-day study indicating a non-significant biological change in rat insulin levels (Brewer & Smith, 1977). No pancreatic effects were seen in subacute inhalation studies in rats or guinea pigs, although pathological lesions were seen in rats exposed (oral) to HCFC-123a, the major impurity in HCFC-123 (see Section 12.2). The NOAEL determined from chronic exposure (inhalation) in rats is 300 ppm (1.9 mg/L).

Classification status

The Approved Criteria (NOHSC, 1998) for severe effects after repeated or prolonged exposure by inhalation require the demonstration of clear functional disturbance or morphological change of toxicological significance at an exposure level ≤ 0.25 mg/L (40 ppm HCFC-123) in a 90-day toxicity study in rats, or equivalent data derived from practical experience. Even if the NOAEL effect for liver effects in rats was 100 ppm, it is considered that the available human case reports and metabolism data provide sufficient evidence of greater sensitivity for humans to hepatic effects. Although potentially reversible, clinical evidence of liver dysfunction has been reported at exposure levels (not further characterised) between 5-50 ppm. This evidence, together with the mechanistic uncertainties regarding the mechanisms of tumour induction in rats, is considered adequate to classify HCFC-123 with risk phrase R48/20 – Harmful: danger of serious damage to health by prolonged exposure through inhalation.

12.3.5 Reproductive effects

No data exist on the effects of HCFC-123 on male or female reproductive functions in humans.

Effects on fertility

In a 2-generation reproductive toxicity study in rats, exposure (inhalation) to HCFC-123 did not influence pre-mating interval, copulation index, pregnancy rate or pup sex ratio of the F_0 and F_1 generations, but was associated with decreased implantation sites among F_1 females at 1000 ppm, a level at which overt maternotoxicity was observed (Hughes, 1994). In a 1-generation study in the same species, exposure (inhalation) to 1000 ppm HCFC-123 had no effect on pregnancy rate, pregnancy duration, number of implantation sites, number of liveborn pups/dam, mean pup weight or litter weight at birth (Heinrich, 1996).

Adverse effects on reproductive tissues, such as testicular Leydig (interstitial) cells have been seen in repeated dose studies at and above 300 ppm HCFC-123 (Kelly, 1975; Malley, 1992; Warheit, 1993) although no histopathological effects on reproductive tissues were seen at 1000 ppm HCFC-123 after 39 weeks in a 2-generation reprotoxicity study (Hughes, 1994).

Perturbations in serum sex hormone levels have also been reported in male rats and guinea pigs (Warheit, 1993). Reduced progesterone levels (F_1 generation only) and elevated LH levels (F_0 generation only) were seen in male rats at 100 ppm and 300 ppm respectively, with a NOAEL of 30 ppm (Hughes, 1994). In male rats of the F_0 generation the LH response to LHRH was inhibited at and above 300 ppm with a NOAEL of 100 ppm and the serum testosterone response was reduced at 1000 ppm although the biosynthesis of sex hormones in the testes was not affected (Sandow et al., 1995b). In another study, exposure (inhalation) to 5200 ppm HCFC-123 for 2 weeks inhibited the testosterone response to an LHRH analogue, but did not impair the LH response to an LHRH analogue and decreased the amount of testosterone in the testes (Sandow et al., 1995a). These effects were not consistent between generations or across studies and have not been linked to any impairment of male reproductive functions or capacity.

Classification status

HCFC-123 does not meet the Approved Criteria (NOHSC, 1998) for effects on fertility (by inhalation).

Effects on development and lactation

In rabbits, developmental effects (increased resorptions and foetal defects) were seen only at doses which caused maternotoxicity, that is, greater than 10,000 ppm (Schroeder, 1989).

In rats, HCFC-123 caused reduced pup growth in the offspring of the F_1 generation at and above 30 ppm, and the F_0 generation, at and above 100 ppm (Hughes, 1994). Reduced pup growth was not considered to be a developmental effect as significant reduction in pup weight was not seen until 7-14 days after birth. Sexual maturation was also slightly delayed in F_1 males (F_0 offspring) at and above 300 ppm. However, the group mean body weight at attainment of sexual maturity was similar to controls, suggesting differences in pup growth rates may account for this delay.

A study in female rats exposed to 1000 ppm HCFC-123 (by inhalation) during pregnancy and lactation used cross-fostering to distinguish between developmental and lactational effects. Pups reared by dams exposed to HCFC-

123 showed reduced growth and decreased serum triglycerides although they had never been exposed to HCFC-123 vapours themselves. The milk of dams exposed to HCFC-123 was of normal quantity and quality but contained significant levels of TFA. TFA was also found in the urine of pups reared by dams exposed to HCFC-123 (Heinrich, 1996).

In 4 lactating monkeys and their infants which were all exposed to 1000 ppm HCFC-123 6 h per day for 21 days, exposure had no effect on infant growth, although the milk of exposed mothers contained HCFC-123 and TFA and blood levels of TFA were higher in exposed infants than in their corresponding mothers (Slauter, 1997). However, substantial levels of HCFC-123 and TFA were detected in the blood of one infant in the control group. If this infant is excluded from the analysis of body weight gains, there is a 10% reduction in the average growth rate of exposed infants.

Classification status

HCFC-123 does not meet the Approved Criteria (NOHSC, 1998) for developmental toxicity. HCFC-123 meets the Approved Criteria for effects on lactation and should be classified with risk phrase R64 – May cause harm to breast-fed babies.

12.3.6 Genotoxicity

The genotoxic potential of HCFC-123 has been studied in a number of *in vitro* and *in vivo* bioassays. Most of these studies were designed to evaluate the genotoxic effects from exposure to HCFC-123 vapour.

HCFC-123 showed no evidence of mutagenicity with *in vitro* bacteria or yeast tests and *in vivo* mouse micronucleus test, and showed no evidence of inducing primary DNA damage by unscheduled DNA synthesis or cell transformation.

Evidence for clastogenicity, from *in vitro* and *in vivo* lymphocyte studies, was conflicting.

Classification status

HCFC-123 does not meet the Approved Criteria (NOHSC, 1998) for mutagenic effects.

12.3.7 Carcinogenicity

No data exist for carcinogenicity in humans following exposure to HCFC-123. Although other structural analogues of HCFC-123 have been shown to cause tumours in animal studies, inadequate evidence exists for carcinogenicity in humans from epidemiological studies (IARC, 1987).

Chronic exposure to HCFC-123 elicited benign tumours (liver, pancreas and testes) in rats at and above 300 ppm (1.9 mg/L). As shown in Table 6, the dose-response curve was non-linear for all tumour types. This suggests that a threshold exposure level can be identified, although the study did not determine a no observed effect level for neoplastic lesions.

As the available data indicate HCFC-123 is non-genotoxic, data relevant to characterising the mechanism for tumourigenicity in animals was reviewed in order to assess its relevance to humans.

Hepatic tumours

Two types of hepatic tumours were observed in the 2-year inhalation study in rats - hepatocellular adenomas and cholangiofibromas.

Hepatocellular adenomas. Several repeated-exposure studies have shown that HCFC-123, its major metabolite TFA and main impurity HCFC-123a, like many other, structurally diverse chemicals, induce peroxisome proliferation in rat hepatocytes (Keller, 1995, 1998; Lewis, 1990; Malley, 1990, 1992; Warheit, 1993). Peroxisome proliferators are generally not genotoxic (IARC, 1995). They activate a nuclear hormone receptor (peroxisome proliferator-activated receptor alpha) that regulates expression of the genes associated with their biological response (Chevalier & Roberts, 1998). They induce hepatocellular proliferation and liver tumours upon prolonged administration to rats and mice through a mechanism that appears to involve the expression of growth factors by hepatic macrophages. The induction of peroxisome proliferation has been proposed as the primary mechanism for hepatocellular tumour induction seen in rats exposed to HCFC-123 (Warheit, 1993). Evidence indicates that primates (including humans) and guinea pigs are significantly less susceptible (in terms of activation of peroxisome proliferator-activated receptor alpha) to peroxisome proliferating substances (Chevalier & Roberts, 1998) and it has been suggested that peroxisome proliferators are unlikely to present a hepatocarcinogenic hazard to humans (Purchase et al., 1994).

Hepatocholangiofibromas. Benign cholangiofibromas (seen in female rats exposed to 5000 ppm) have generally not been reported for other peroxisome proliferating substances (exceptions being thioacetamide and ethionine (ECETOC, 1996)) and hence peroxisome proliferation does not appear to be an obvious mechanism for this tumour type.

The cholangiofibromas induced by HCFC-123 were atypical glandular structures lined by intestinal-like epithelium and surrounded by dense connective tissue. Similar lesions have been produced by various non-genotoxic chemicals including chloroform and furan. These lesions were usually associated with significant hepatocyte necrosis and regenerative cell proliferation and were associated with increased growth factor expression or uptake (Jamison et al., 1996). They appeared to have the potential to develop into malignant tumours which closely resemble the intestinal type of adenocarcinoma that occurs in human liver and gallbladder (Elmore & Sirica, 1993).

The significance of the cholangiofibromas seen in rats has been questioned on statistical grounds. Although life table analysis of these tumours showed a non-significant result (P = 0.063), this value is close to the conventional cut off (P = 0.05) and as such biological significance can not be discounted. Using the Fischer's exact pairwise test for this tumour P (2-tailed) equals 0.0002, which is highly significant and consistent with a threshold effect rather than a linear dose-response effect.

Pancreatic tumours

HCFC-123 exposure was associated with a dose-related increase in benign acinar cell adenomas in male rats. It is reported that other hepatic peroxisome proliferators also induce pancreatic acinar cell adenomas (Tucker & Orton, 1995). A concomitant increase (dose-related) in acinar cell focal hyperplasia seen in male rats indicate a tenuous association of this tumour type with peroxisome proliferation as dose response correlations for focal hyperplasia and peroxisomal response in rodents are reportedly poor (Budroe et al., 1992). Indeed, a slight increase in pancreatic cell proliferation rate (CPI) was seen in rats exposed to HCFC-123 without an increase in pancreatic peroxisome proliferation (Warheit, 1993). In addition, the apparent lack of accumulation or covalent binding of HCFC-123 and metabolites in pancreatic tissue (Dekant, 1993) indicates that tumourigenicity is unlikely to be associated with direct cellular interaction. Therefore, other mechanisms for tumour induction would appear to be involved.

WY-14643, a known peroxisome proliferator which induces hepatocellular, pancreatic acinar cell and Leydig cell adenomas in rats and does not induce peroxisomes in the pancreas (or Leydig cells), has been shown to cause a mild but sustained increase of around 40% in CCK levels that is secondary to chronic hepatocellular damage and cholestasis (Obourn et al., 1997). CCK has been shown to stimulate pancreatic growth and acinar cell carcinogenesis in animals and has also been implicated in the aetiology of human pancreatic cancer (Woutersen et al., 1991). Compared with controls, serum CCK was increased by 27% in male rats exposed to 18,000 ppm HCFC-123 by inhalation for 4 weeks, by 57% in male rats fed a diet containing 7,500 ppm TFA for 4 weeks (Warheit, 1993) and by 217% in male and 50% in female rats exposed to 1000 ppm HCFC- 123 by inhalation for 39 weeks (Hughes, 1994), although these increases failed to reach statistical significance.

The development of pancreatic acinar cell hypertrophy, hyperplasia and adenomas in the rat is modified by steroids (stimulated by testosterone and inhibited by oestradiol), although the mechanism is unknown and may be direct or mediated through a peptide hormone (Longnecker & Sumi, 1990; Woutersen et al., 1991). Compound-related perturbations in levels of testosterone, oestradiol and LH and in the pituitary response pattern of gonadotropins and prolactin have been reported in rats exposed to HCFC-123 (Hughes, 1994; Sandow, 1995a; Sandow, 1995b; Warheit, 1993) and may account for the pronounced sex difference in the incidence of pancreatic lesions in the 2-year bioassay.

Testicular tumours

Leydig (interstitial) cell tumours in rats have been reported for a large number of substances including hepatic peroxisome proliferators (Cook et al., 1993). The evidence available indicates that hepatic peroxisome proliferating substances do not significantly affect Leydig cell peroxisome proliferation (despite known levels of peroxisomes in Leydig cells) or testicular cell proliferation rate (Biegal et al., 1992; Warheit, 1993). In addition, other factors such as the apparent lack of covalent binding of HCFC-123 and metabolites in testes (Dekant, 1993) and the lack of a dose-response relationship (with HCFC-123 elicited Leydig cell tumours) indicate that direct cellular damage or peroxisome proliferation are unlikely to be primary mechanisms in tumour induction.

In male rats, exposure to HCFC-123 has been shown to cause perturbations in serum oestradiol, testosterone (Warheit, 1993), LH and progesterone (Hughes, 1994) in addition to necrosis of testicular germ cell epithelium and tubular atrophy (at approximately 18,000 ppm HCFC-123) (Warheit, 1993). HCFC-141b and HFC-134a, which are structural analogues of HCFC-123, both induced Leydig cell tumours in chronic toxicity studies in the rat, but unlike HCFC-123 they do not induce peroxisome proliferation (Keller, 1995). However, in male rats exposed to concentrations which were similar to the highest exposure level in the respective 2-year bioassays, HCFC-123, HCFC-141b and HFC-134a all caused a reduced response of serum prolactin and serum testosterone to stimulation with mono-iodo-tyrosine and buserelin (an LHRH analogue) and a marked decrease in the quantity of testosterone in the testes (Sandow et al., 1995a). In rats, but not in man, a decrease in prolactin causes a decrease in Leydig cell LH receptor number and thus a decrease in testosterone production (Clegg et al., 1997). In both species decreased testosterone results in increased LH levels. Intermittent exposure to HCFC-123 could lead to fluctuations in prolactin and testosterone that in turn could result in transient changes in LH and, with time, in Leydig cell hyperplasia and adenomas. Such effects indicate that HCFC-123 belong to the large number of non-genotoxic substances that induce Leydig cell adenomas in rats through interference with the hypothalamic-pituitary-testicular axis at various points, setting off a chain of events that may range from a sustained increase in circulating LH to a situation where changes in LH are small or are transient in expression (Clegg et al., 1997).

Some peroxisome proliferators have been shown to increase serum levels of oestradiol in adult male rats through a decrease in hepatic oestradiol catabolism or an increase in hepatic conversion of androgens to oestrogens (Liu et al., 1996). However, oestradiol does not induce Leydig cell adenomas in rats (Clegg et al., 1997).

Overall assessment of carcinogenic hazard

The NOAELs, possible mechanisms and relevance to humans of the four tumour types found in rats exposed to HCFC-123 for 2 years are summarised in Table 11.

The available evidence indicates that the benign hepatocellular adenomas seen in rats exposed to HCFC-123 are related to the activation of peroxisome proliferator-activated receptor alpha, which is a mechanism to which humans are unlikely to be susceptible.

The mechanistic significance of benign hepatocholangiofibromas in female rats is unclear as this tumour type is not associated with peroxisome proliferation or hormone perturbation, however its biological significance is confirmed by pre-neoplastic lesions (cholangiofibrosis) seen at 12 months in the same study. There is limited evidence from animal studies (Jamison et al., 1996) to suggest that this tumour type is associated with significant hepatocyte necrosis and regenerative cell proliferation that are relevant only at high dose/exposure levels. Indeed, statistical interpretation of the data support the existence of a threshold level for this effect of HCFC-123 (1000-5000 ppm).

Table 11 – Possible mechanisms and relevance to humans of tumours elicited in rats

Tumour type	*NOAEL (from Table 6)*	*Possible mechanisms*	*Relevance for humans*
Hepatic adenoma	5000 ppm in males. Not determined in females.	Activation of peroxisome proliferator-activated receptor alpha leading to increased expression of hepatic growth factors	Unlikely
Cholangiofibroma	5000 ppm in males. 1000 ppm in females.	Hepatic cell necrosis and regenerative cell proliferation leading to increased growth factor expression or uptake	Not excluded
Pancreatic acinar adenoma	Not determined	Increase of CCK levels secondary to chronic hepatocellular damage and cholestasis	Not excluded
Leydig (interstitial) cell adenomas	Not determined	Fluctuations in prolactin levels	None
		Other endocrine disruptions	Not excluded

Despite limited epidemiological evidence to suggest that the proposed hormonal mechanism (CCK stimulation of pancreas growth) is of questionable relevance for human pancreatic cancers (Messina & Messina, 1991) and despite the fact that acinar cell cancers are not common in humans (by far the greatest number of human pancreatic tumours are of the ductal type (Woutersen et al., 1991)), it must be assumed that, until more is known about the mechanism for acinar cell tumour induction in animals and humans (particularly the role of CCK), the pancreatic adenomas found in rats may have some predictive value for human carcinogenicity.

Benign Leydig (interstitial) cell adenomas are common in ageing rats and strongly associated with senile endocrine disturbances. In contrast to the rat, Leydig cell tumours in men are extremely rare, representing less than 3% of all testicular neoplasms (Mostofi & Price, 1973). In general, substances that cause hepatic peroxisome proliferation in rats also cause the development of Leydig cell adenomas upon long-term administration. Although a causal relationship between peroxisome proliferation and Leydig cell adenomas has not been proven, it has been suggested that the two effects are linked. As substances that are peroxisome proliferators in rats have little, if any, effect on human liver it was inferred that HCFC-123-induced Leydig cell adenomas were of questionable relevance for humans. However, HCFC-141b and HFC-134a, which are structural analogues of HCFC-123, both induced Leydig cell tumours in chronic toxicity studies in the rat, but are not peroxisome proliferating substances (Kelly, 1995). Rather, HCFC-123, HCFC-141b and HFC-134a all interfere with the hypothalamic-pituitary-testicular axis in ways which could lead to fluctuations in prolactin and testosterone that in turn could result in transient changes in LH and, with time, induce Leydig cell hyperplasia and adenomas (Sandow et al., 1995a). Although

prolactin fluctuations would not be of concern in men (Clegg et al., 1997), the effects of HCFC-123 on the sex hormone system are complex and, in the absence

Design elementDesign elementof data from studies in primates, the increased incidence of Leydig cell adenomas in rats following prolonged exposure to HCFC-123 cannot be dismissed with respect to its relevance for humans.

For all three tissues in which tumours occur, the cell type (except cholangiocellular tissue) has been a site of tumourigenic activity for other peroxisome proliferators (including hypolipidaemic drugs) (Tucker & Orton, 1995). As this triad of tumour types have not been reported in epidemiological data on hypolipidaemic drugs (classic peroxisome proliferating substances), it has been hypothesised that hepatic, testicular and pancreatic tumours seen in rodents are not relevant to humans. However, such a conclusion should be viewed with caution as epidemiological data on hypolipidaemic drugs only exist for clofibrate and fenofibrate, neither of which produce testicular or pancreatic tumours in animal studies. In addition, such human studies are considered inconclusive due to the short period of exposure and follow-up (Bentley et al., 1993).

Overall, indications are that the primary mechanism(s) of tumourigenicity for HCFC-123 is non-genotoxic (epigenic) and that activation of peroxisome proliferator-activated receptor alpha, chronic hepatocellular injury and cholestasis and interference with the hypothalamic-pituitary-testicular axis may all be involved to some degree. Such a multi-factorial mechanism might account for the sex differences[2] and the lack of target organ specificity[3] with respect to HCFC-123 elicited tumours in rats.

Hepatocyte growth induction by peroxisome proliferators and fluctuations in prolactin levels in males are mechanisms of little, if any, relevance for humans. However, HCFC-123 also interferes with the hypothalamic-pituitary-testicular axis at other points, which could be relevant for humans. Furthermore, there are now reports that repeated exposure to HCFC-123 may cause hepatocellular injury and, in some cases, cholestasis in humans. In consequence, until further data become available regarding the mechanism of HCFC-123 induced tumours, particularly with respect to the induction of cholangiofibroma, pancreatic adenoma and Leydig (interstitial) cell adenoma, it must be concluded that findings in rats may have some relevance for humans.

Classification status

HCFC-123 meets the Approved Criteria (NOHSC, 1998) for carcinogenic effects (Category 3[b]) and should be classified with risk phrase R40 – Harmful: possible risk of irreversible effects. It should be noted that, according to the Approved Criteria, this classification is provisional and further studies are necessary before a final decision can be made.

[2] Sex differences in peroxisome proliferation with HCFC-123 do not appear to be related to sex differences in tumour incidence.

[3] Non-genotoxic carcinogens tend to be organ, species and sex specific.

13. Human Health Risk Characterisation

In order to assess the health risks associated with the use of HCFC-123 it is necessary to integrate information on human exposure with human health hazards. This process, referred to as 'risk characterisation', provides the basis for evaluating occupational health and safety risk management strategies, including the setting of exposure standards.

13.1 Design elementCritical effects and exposures

13.1.1 Effects from single exposure

Effects identified for acute exposure to HCFC-123 are eye irritation, liver toxicity, CNS depression, cardiac sensitisation and asphyxiation. The major route of exposure for these effects (except eye irritation) is inhalation.

Critical effects associated with acute HCFC-123 exposure are liver toxicity, CNS depression and cardiac sensitisation, all of which have been seen in humans from exposure to structural analogues of HCFC-123.

In a single acute inhalation study carried out in guinea pigs, liver necrosis was seen at the lowest test exposure of 1000 ppm HCFC-123. Lesions in this study were similar to those seen in guinea pigs but not rats (exposed to around 9000 ppm and 18,000 ppm HCFC-123 respectively) in a 28-day study. A similar hepatotoxicity profile to HCFC-123 (Warheit, 1993) was seen in rats and guinea pigs from acute exposure to halothane (see Section 12.1.1). Although, there is evidence to suggest that HCFC-123 may exhibit a similar acute toxicological profile to halothane in humans, it should be noted that the incidence (Marit et al., 1994) of halothane elicited hepatitis in humans is around 1 in 10,000 for the severe necrotic form and around 20% for the mild form at anaesthetic concentrations, at and above 10,000 ppm. By analogy to halothane, humans would be expected to be less sensitive to the hepatic effects seen in animals after a *single* exposure to HCFC-123.

The most sensitive study for CNS effects (carried out in rats) demonstrated a no effect level of 2500 ppm HCFC-123. There are no data to suggest that humans are likely to be more or less sensitive than rats with respect to CNS effects.

No data are available on HCFC-123 exposure levels associated with cardiac sensitisation in humans, but a no effect level and an EC_{50} for cardiac sensitisation in dogs was determined at 10,000 ppm and 19,000 ppm HCFC-123 respectively (Trochimowicz & Mullin, 1973). The available evidence (US EPA, 1994b) indicates that cardiotoxic levels obtained from dog studies are likely to be conservative with respect to extrapolation to humans.

All critical effects reported from acute exposure to HCFC-123 are essentially reversible in nature, and evidence from studies in humans and animals with halothane suggests that humans would be less sensitive to acute HCFC-123-

Design elementelicited hepatotoxicity than animals (Marit et al., 1994; Ray & Drummond, 1991). However, it would seem prudent, based on the available data, to assume that a single inhalational exposure to HCFC-123 above 1000 ppm (6.3 g/m^3) may present a human health risk.

13.1.2 Effects from repeated exposure

Reversible liver effects have been reported in humans following repeated exposure to HCFC-123. Clinical findings indicated that these effects varied from mild liver cell injury to focal liver necrosis and cholestasis. Where exposure levels were measured, they ranged from 5-500 ppm HCFC-123.

In animals, critical effects identified from repeated exposure to HCFC-123 by inhalation were seen in liver, pancreas and testes. In rats, retarded pup growth has been identified as a lactational effect, with a LOAEL of 30 ppm for dams exposed to HCFC-123 throughout a 2-generation reproductive toxicity study. HCFC-123 and/or its major metabolite TFA have been shown to be excreted in breast-milk of monkeys and rats.

Liver effects have been seen in rats, guinea pigs, dogs and monkeys and have been reported in humans for other halogenated ethanes, including the HCFC-123 analogue, halothane. Therefore, hepatotoxicity would appear to be the adverse effect of most relevance to humans and also represents the most sensitive effect with respect to detection of chronic tissue damage. The lowest dose causing liver damage (histological evidence) in repeated dose studies in animals was 300 ppm, with a NOAEL of 100 ppm. The available evidence indicates that humans metabolise HCFC-123 at a faster rate than rats and may develop biochemical signs of liver injury such as elevated AST and ALT at exposure levels that are considerably lower than the NOAEL in animals.

Benign liver tumours (in rats) seen at the lowest dose tested (LOAEL = 300 ppm) following chronic exposure to HCFC-123, may well be a secondary consequence of the hepatocellular effects seen at this exposure level. Indeed, there is evidence for peroxisome proliferating substances, that both toxic and proliferative phenomena (for example, CPI) occur in the interval between liver enlargement and tumour production (Grasso & Hinton, 1991).

The available evidence indicate that the primary mechanism(s) of tumourigenicity is non-genotoxic (epigenic) and include activation of peroxisome proliferator-activated receptor alpha in hepatocytes, chronic hepatocellular injury and cholestasis as well as interference with the hypothalamic-pituitary-testicular axis. Although human liver effects have been reported at a lower range of exposures, the NOAEL for hepatic lesions from repeated-dose animal bioassays (inhalation) is 100 ppm HCFC-123. Furthermore, changes indicative of peroxisome proliferation and hormone perturbation were not significant at this exposure level (Hughes, 1994). Therefore, it appears valid to assume that a threshold exists for tumourigenicity for HCFC-123, even if a NOAEL for all neoplastic lesions was not identified in the 2-year bioassay.

13.2 Occupational health risks

In Australia, occupational exposure to HCFC-123 is limited to workers engaged in the transport, handling, storage and filling of refrigerant or extinguishant

containers or calibration gas cylinders, workers involved in chiller and extinguishant system installation, maintenance and testing, including technicians involved in calibration of alarms or detectors used in refrigeration plants, and firefighters. Occupational health risks for all workers potentially exposed to HCFC-123 refrigerant or extinguishant can be divided into acute and chronic risks. The content of HCFC-123 in calibration gas (around 20 or 60 mg per cylinder) is too low to pose any occupational health risks during alarm calibration activities.

13.2.1 Acute health risks

Refrigerant exposure

Although breathing zone levels of several hundred ppm HCFC-123 have been measured following spills, risks of critical health effects (CNS depression, liver toxicity and cardiac sensitisation) from acute HCFC-123 exposure are considered to be low during normal transport, handling and use, including chiller maintenance. Similarly, risks of asphyxiation from acute exposure to HCFC-123 are considered even lower and would only exist following a catastrophic leakage of chiller refrigerant or where refrigerant leakage was allowed to accumulate in a confined space or low lying areas, for example, pits.

Extinguishant exposure

Although information on exposure to HCFC-123 during installation and testing of HCFC extinguishant blends was not available for assessment, exposures and hence acute health risks are expected to be low. Similarly exposures during normal transport and handling (including filling operations) are also expected to be low.

Apart from the remote possibility of occupants remaining in the hazard zone during fixed extinguishant discharge, limited human exposure to total flooding extinguishants would be expected, due to their automated mode of discharge and intended discharge into non-occupied areas. However, the design level of HCFC blend extinguishant in such systems may lead to 2900 ppm HCFC-123 in an enclosed unventilated area, which may present an acute health risk to workers remaining in the hazard zone. Concomitant exposure to other HCFCs in the blend may present an increased risk due to additive effects.

The potential for exposure to HCFC-123 from discharge of portable extinguishers is much greater than from total flooding systems due to the manual mode of operation. Apart from failure of SCBA respirators, risks to professional firefighters would be expected to be minimal due to the deployment of full protective equipment. Risks to other workers without personal protective equipment using such extinguishants would however be considerably higher, particularly where the extinguishant is discharged into a confined working area. Although monitoring data indicates that levels of HCFC-123 from portables containing HCFC blends are unlikely to present a health risk *per se*, concomitant exposure to other HCFCs in the extinguishant blend may increase this risk due to the additive effects of other ingredients, particularly, CFCs and HCFCs.

In the overall assessment of risk, consideration should be given to confined spaces and duration of exposure.

NAF P-III and NAF S-III contain about 4% 4-isopropenyl-1-methylcyclohexene (limonene), a highly volatile compound with a low odour threshold which is highly reactive towards free radicals and oxidising agents. Limonene is added to reduce the formation of toxic combustion products from the HCFC components of NAF P-III and NAF S-III, but may also aid in leak detection. The toxicity of limonene has been reviewed by IPCS (1998).

Sensitive populations

There is limited evidence to suggest that some workers may be at greater risk from acute exposure to HCFC-123 than others (Aviado & Micozzi, 1981). Individuals with pre-existing cardiovascular disease or individuals using medications containing adrenaline or catecholamines (sympathomimetic medications) may be more sensitive to cardiac effects elicited by HCFC-123.

Ethanol has been shown to be an effective inducer of the CYP 2E1 isoform of cytochrome P450 (Klotz & Ammon, 1998), which is involved in the biotransformation of HCFC-123 in humans. As such, it is possible that regular alcohol consumption may accelerate the formation of metabolites from HCFC-123 and aggrevate adverse health effects from repeated exposure to the chemical.

13.2.2 Chronic health risks

Refrigerant exposure

Exposures from drum leakage and spills will generally be infrequent. Therefore, the risk of chronic health effects from normal transport and handling is considered negligible. Similarly, the content of HCFC-123 in calibration gas (around 20 or 60 mg per cylinder) is too low to pose any occupational health risks during alarm calibration activities.

The population at risk from chronic exposure to HCFC-123 are chiller maintenance technicians. The potential for chronic exposure of maintenance technicians to HCFC-123 refrigerant is dependent on the number of hours spent at chiller installations running on HCFC-123 and the types of maintenance activities carried out. Results from personal monitoring studies indicate that the TWA exposure during a normal working shift is generally 1-5 ppm, even where peak levels in excess of 100 ppm are encountered[1] during the working shift.

In PEC4 (NICNAS, 1996), the approach used in assessing the risk of chronic effects in workers was that of determining the 'margin of safety', that is, chronic N(L)OAEL divided by the measured TWA occupational exposure. The NOAEL determined for chronic effects in animals is 100 ppm (see Section 13.1.2) and levels of exposure are 1-5 ppm (TWA). Therefore, the 'margin of safety' is 20-100 for chronic occupational effects. This range of margin was considered sufficient when taking into consideration other interrelated factors such as inter- and intra-species differences and the confidence and adequacy of the animal database. However, recent information indicates that humans may develop biochemical signs of liver injury such as elevated AST and ALT at exposure levels that are up to 20-fold lower than the animal NOAEL. Although such

[1] Such levels do not usually last for more than a few minutes and would not be expected to be encountered more than three times during a normal working shift (6-8 h).

effects are associated with mild or no clinical illness and are likely to be reversible upon termination of exposure, the risk of liver effects in chiller maintenance technicians from repeated exposure to HCFC-123 may be significant and further research is required to investigate this.

Extinguishant exposure

Exposures from cylinder leakage and spills will generally be infrequent and therefore the risk of chronic health effects from normal transport and handling (including filling operations) is considered negligible. Similarly, exposure to HCFC-123 during extinguishant installation and testing is also likely to be infrequent, taking into account the specialist use of HCFC blend extinguishants. However, should these extinguishants be used on a much larger scale, the potential risk to maintenance workers should be further investigated by characterising the duration and extent of worker exposure.

Despite the potential for high level exposures to HCFC-123 during extinguishant discharge, occupational exposure to either streaming or total flooding agents would be expected to be infrequent. In addition, modern SCBA equipment used by professional firefighters affords a high level of protection (protection factor[2] of at least 10,000 (Burgess & Crutchfield, 1995)). The removal of facepieces following fire extinction may result in exposure to residual HCFC-123.

In view of the low frequency of discharges of HCFC blend extiguishants, the risk of chronic health effects from HCFC-123, in both professional firefighters and other workers using extinguishants, is considered to be extremely low.

13.3 Health risks from exposure to products of combustion

In addition to risks from exposure to HCFC-123, a potential also exists for health risks from exposure to products of combustion (POCs). This is particularly relevant for firefighters using extinguishants containing HCFC-123.

For HCFC-123, POCs are reported to include phosgene, hydrogen chloride and hydrogen fluoride. No data were available on levels of phosgene from extinguishant pyrolysis. Levels of hydrogen chloride and hydrogen fluoride around their exposure standard levels were measured in a study with the streaming agent Halotron-I. Products resulting from reaction of the extinguishant with combusting materials may present an additional hazard.

The nature and severity of potential health effects from the above pyrolysis reactions will be unpredictable because of the potentially wide variation in the concentration of HCFC-123 in extinguishant blends, the amount discharged, the type and size of fire.

13.4 Assessment of public exposure

Under normal conditions, the public are unlikely to be exposed to HCFC-123, given that the chemical is enclosed within sealed systems during its working life when used as a refrigerant and as a fire extinguishant. Public or occupational exposure to peak levels of several hundred ppm during chiller maintenance would

[2] The US NIOSH recommends a protection factor (PF) of 10,000 for the pressure-demand, SCBA respirators used by fire fighters.

not be expected to cause acutely toxic effects. In addition, such leakage is likely to be confined to air-conditioning plant rooms or areas of restricted public access.

Significant short-term exposure of the public to HCFC-123 could occur after a transport accident, given its high vapour pressure. In such circumstances, prompt isolation of the spill site would be required to minimise the risk to the public. Significant public exposure could also arise from activation of a fire extinguishing system within a building from which the occupants had not been evacuated. Under these conditions, airborne HCFC-123 concentrations could attain 1000 ppm, which would be sufficient to cause acute effects. However, transport accidents and extinguishant discharges involving the public are expected to be rare events.

Although it appears that humans are more sensitive than experimental animals to chronic exposure, the likelihood of repeated exposure to the public would be extremely rare.

14. OHS Risk Management

The key elements in the management of occupational health and safety risks from exposure to a hazardous substance include:

- workplace control measures;
- emergency procedures;
- hazard communication/training;
- exposure standards and air monitoring; and
- health surveillance.

In this Section, measures currently employed and/or recommended to reduce occupational health and safety risks associated with the handling and use of HCFC-123 have been assessed. The information reviewed includes national and international standards and codes of practice as well as training materials, guidance documents, labels and MSDS developed by manufacturers and users. No information was available on measures relating to HCFC-123 calibration gases.

14.1 Workplace control measures

HCFC-123 is classified as a hazardous substance in accordance with the NOHSC Approved Criteria (NOHSC, 1998). Under the NOHSC *National Model Regulations and Code of Practice to Control Workplace Hazardous Substances* (NOHSC, 1994c), control measures to reduce exposure must be implemented to minimise risks to health and safety. In particular, controls should be implemented to minimise inhalation exposure to HCFC-123 vapour.

In general, the control of worker exposure to any hazardous substance should be achieved through the following hierarchy of control strategies:

- elimination;
- substitution;
- isolation;
- engineering controls/equipment design;
- safe work practices; and
- personal protective equipment.

Control measures are not mutually exclusive and effective control usually requires a combination of these measures.

It is not within the scope of this report to document each and every control measure assessed. However, all measures made available for assessment were evaluated in order to identify the essential elements of the above control strategies.

14.1.1 Elimination and substitution

Refrigerant

In the air-conditioning industry HCFC-123 is currently being used as an interim replacement for the refrigerant CFC-11 which is being phased out due to its high ozone-depleting potential (ODP) under the Montreal Protocol. Because HCFC-123 is also an ozone-depleting substance (low ODP), it is to be phased out under the Montreal Protocol by 2030 or earlier if a more suitable, long term-replacement is found.

Currently, HCFC-123 is the only suitable 'drop-in'[1] alternative to CFC-11 use in low pressure centrifugal chillers, based on a number of criteria which include thermodynamic properties, flammability, compatibility with lubricants and other materials used to fabricate and service refrigeration systems. Based mainly on environmental grounds, its use as an interim replacement for CFC-11 has been endorsed by Environment Australia (EA) and the US EPA.

Due to lack of human data it is unclear whether HCFC-123 is less hazardous than CFC-11 based on health effects. In general, substitution requires great care as other refrigerants may not necessarily offer a greater degree of safety and indeed many refrigerants in current use present additional hazards (Calm, 1994; Hoffman, 1990).

Extinguishant

In the firefighting industry HCFC-123 blends (NAF S-III and NAF P-III) are currently being used as interim replacements for Halons 1301 and 1211, the use of which have been phased out according to the Montreal Protocol.

With regard to toxicity, it is reported that NAF S-III is more toxic than Halon 1301 with respect to lethality in animal bioassays but less toxic with respect to cardiac effects (NFPA, 1996). No data on comparative toxicity were available for NAF P-III and Halon 1211.

It should be emphasised that other so-called 'inert' extinguishants are extremely hazardous, for example CO_2 (asphyxiation and CNS depressant effects), at the concentrations required for fire protection. Alternatives to HCFC extinguishant blends should be considered carefully to ensure that risks to health and safety are not increased.

14.1.2 Isolation

Refrigerant

HCFC-123 is isolated by virtue of its containment within the sealed chiller system where relief points are vented to atmosphere. Isolation of the refrigerant is also maintained during chiller maintenance activities by the use of portable refrigerant recovery devices.

[1] Suitable for direct replacement of CFC-11 pending retrofit of chiller, for example, gasket/seal change.

Extinguishant

Extinguishants are contained in pressurised cylinders which are closed systems and as such are isolated from the workplace. Total flooding (fixed) systems are further isolated from the workplace in that the extinguishant cylinders are located away from the work areas. In addition, measures are usually taken to confine extinguishant discharge to a particular 'hazard area', thus preventing exposure of personnel located in other work areas.

14.1.3 Engineering controls, safe work practices and personal protective equipment

Sources of occupational exposure have been identified and assessed (PEC4, Section 8). Thus further options, such as engineering controls, safe work practices and personal protective equipment should be considered to reduce such exposures. In addition, equipment design and specification is of particular importance in controlling exposure to refrigerants and extinguishants. With regard to reducing health risks from HCFC-123 exposure, control measures should focus on reducing exposure by inhalation.

Refrigerant

Control measures introduced to protect workers from adverse health effects from HCFC-123 refrigerant need to address hazards from chronic exposure to low levels of refrigerant in addition to hazards from acute high level exposures. Current control measures employed in the air-conditioning industry would appear to be sufficient to maintain TWA levels (8 h) below 5 ppm HCFC-123, however peak levels in excess of 100 ppm have been recorded during certain chiller maintenance activities. In general, such excursion levels can be reduced by paying particular attention to control measures aimed at ensuring efficient refrigerant recovery during transfer and adherence to safe work practices during maintenance and repair procedures, particularly during leak test operations.

A number of control measures were identified as integral to reducing occupational health risks during refrigerant handling and use, and these are listed in Appendix 2. The majority of the control measures are embodied in the following codes and standards, which currently comprise the fundamental reference documentation used by chiller maintenance technicians in Australia:

- Safety Code for Mechanical Refrigeration (ASHRAE, 1994).
- The Australian Refrigeration & Air Conditioning Code of Good Practice (AFCAM, 1997).
- Refrigerating Systems (AS/NZ 1677 (1998)) (Australian Standard, 1998).

Safety Code for Mechanical Refrigeration (ASHRAE, 1994). Developed by the American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE) in conjunction with the American National Standards Institute (ANSI), this code (referred to as ASHRAE Standard 15) provides information relating to requirements for equipment design, installation, operation and maintenance of air-conditioning systems. Some aspects of refrigerant hazards (including HCFC-123) are also addressed. Coverage of engineering controls and equipment design is fairly extensive, particularly with respect to pressure relief

Design elementDesign elementDesign elementDesign elementDesign elementdevices and mechanical ventilation. Safe working practices and personal protective equipment are dealt with in less detail.

The Australian Refrigeration and Airconditioning Code of Good Practice (AFCAM, 1997). Developed by the Australian Association of Fluorocarbon Consumers and Manufacturers (AFCAM) in 1990 and revised in 1992 and 1997, Code HB40.1-1997 provides information on control measures that assist in the reduction of emissions into the atmosphere of refrigerants which deplete the ozone layer or contribute to global warming. This code is not exhaustive and does not constitute a technical design document and as such the authors recommend that it is used in conjunction with other existing codes and standards. The code covers engineering controls and equipment design, installation and routine servicing protocols (including leak testing), requirements for refrigerant recovery and disposal, and refrigerant handling and storage.

Refrigerating Systems (AS/NZ 1677 (1998)) (Australian Standard, 1998). The Australian Standard AS 1677 – *Refrigerating Systems* (1986) referred to in PEC4, Section 14.1.3 has been superseded by Australian/New Zealand Standard AS/NZS 1677 (1998) (Standards Australia, 1998). The updated standard incorporates relevant features from standards produced by ASHRAE and ISO and is divided into three parts, which cover refrigerant classification, safety requirements for fixed applications and safety requirements for mobile applications. Part 2 specifies fundamental safety requirements, in terms of the design, construction, installation and inspection of refrigerating appliances in institutional, public assembly, residential, commercial and industrial occupancies. It includes requirements for ventilation, refrigerant leak detectors and provision of personal protective equipment.

Overall remarks. Not withstanding the different requirements, aims and scope of the above documents, specific areas of risk management (including control measures) were identified as either not being addressed or lacking details in some or all of the documents[2]. In summary these are:

- safety requirements/precautions;
- procedures for refrigerant transfer and refrigerant/water leak testing;
- specifications/requirements for purging equipment;
- criteria and testing specifications for monitoring equipment, alarms and mechanical ventilation;
- restrictions/requirements (including incompatible materials) for HCFC-123 retrofits;
- use and specification of personal protective equipment (other than SCBA); and
- details of emergency procedures and training requirements.

Extinguishant

Control measures introduced to protect workers from adverse health effects from HCFC-123 in fire extinguishants need to address hazards from acute high level exposures, as chronic exposure to HCFC-123 is unlikely. Such exposures are

[2] It should be noted that these deficiencies were identified (in PEC4) in the draft or superseded versions of both the AFCAM Code and AS/NZS 1677.

unlikely to result during transport, handling, filling and installation/testing operations.

Firefighters and emergency personnel represent the population at most risk from exposure to HCFC-123 from portable extinguishants. Control measures introduced to reduce exposure to professional firefighters rely mainly on personal protective equipment (the selection and specification of which is dealt with by the appropriate authorities). However other workers using portable extinguishers will be reliant on hazard communication, for example, training and labels. Engineering controls aimed at reducing HCFC-123 exposures to workers from total flooding systems are pre-discharge alarms, safety interlocks and controlling the discharge, that is, compliance with design concentration. As with portable extinguishers hazard communication, including warning signs and training/drills will help minimise risks of exposure.

A number of control measures were identified as integral to reducing occupational health risks during extinguishant (total flooding and streaming agents) handling and use, and these are listed in Appendix 3. The control measures in Appendix 3 are embodied in the following codes/standards, which currently comprise the fundamental reference documentation for HCFC blend fire extinguishants used in Australia:

- US Standard on Clean Agent Fire Extinguishing Systems (NFPA, 1996).
- Australian/New Zealand Standard AS/NZS 4214.5 - *Gaseous Fire Extinguishing Systems - NAF S-III (HCFC Blend A) Total Flooding Systems* (Standards Australia, 1995c).
- Australian/New Zealand Standard AS/NZS 4214.1 - *General Requirements for Gaseous Fire Extinguishing Systems* (Standards Australia, 1995b).
- Australian/New Zealand Standard AS/NZS 4214.12 - *Maintenance of Fire Protection Equipment - Gaseous Fire Extinguishing Systems* (Standards Australia, 1995d).
- Australian/New Zealand Standard AS/NZS 1841.7 - *Portable Fire Extinguishers – Specific Requirements for Vaporizing-liquid Type Extinguishers* (Standards Australia, 1997b).
- The FPIAA *Code of Practice for the Design, Installation, Inspection and Testing of Gaseous Fire Extinguishants* (FPIAA, 1995).

US Standard on Clean Agent Fire Extinguishing Systems (NFPA, 1996). Developed by the US National Fire Protection Association, this standard (referred to as NFPA 2001) provides information on new total flooding agents (including NAF S-III) developed to replace Halon 1301. This standard addresses the design, installation, testing, maintenance and operation of total flooding systems and hazards from exposure to replacement extinguishants and their combustion products. With regard to control measures, the standard addresses extinguishant use and limitations; safety requirements; extinguishant storage; equipment specification and design (including detection, actuation, alarm and control systems); pressure relief venting; requirements for maintenance and testing.

Australian/New Zealand Standard - Gaseous Fire Extinguishing Systems - NAF S-III (HCFC Blend A) - Total Flooding Systems (Standards Australia, 1995c). Developed by the Standards Associations of Australia and New Zealand, this standard addresses the requirements for equipment design and installation

and commissioning of gaseous extinguishant (fixed) systems and extinguishant identification, labelling and hazards (including combustion products). Maintenance requirements are the subject of AS/NZS 1851.12 (1995) (see below). With regard to control measures, this standard deals with extinguishant use and limitations, safety requirements/precautions, extinguishant storage, equipment specification and design, requirements for pressure relief venting and procedures and requirements for testing.

Australian/New Zealand Standard - General Requirements for Gaseous Fire Extinguishing Systems (Standards Australia, 1995b). Developed by the Standards Associations of Australia and New Zealand, this standard addresses the general requirements for gaseous extinguishant (fixed) systems and extinguishant agents and covers similar information as AS/NZS 4214.5 (1995) (see above) with the exception of the inclusion of control and actuation systems in this code.

Australian Standard/New Zealand Standard - Maintenance of Fire Protection Equipment - Gaseous Fire Systems (Standards Australia, 1995d). Developed by the Standards Associations of Australia and New Zealand, this standard addresses the maintenance requirements for gaseous fire extinguishing (fixed) systems and contains information on installation, inspection and testing. With regard to control measures, this standard deals exclusively with procedures for testing.

Australian/New Zealand Standard - Portable Fire Extinguishers – Specific Requirements for Vaporizing-liquid Type Extinguishers (Standards Australia, 1997b). Developed by the Standards Association of Australia and New Zealand, this standard addresses the general requirements for the charge and marking of vaporising-liquid portable fire extinguishers. It does not specifically address HCFC-123 Blend C (NAF P-III).

The FPIAA Code of Practice for the Design, Installation, Inspection and Testing of Gaseous Fire Extinguishants (FPIAA, 1995). Developed by the Fire Protection Industry Association of Australia (FPIAA)[3] this code provides information on controlling emissions of ozone-depleting extinguishants. The code covers engineering controls and equipment design, installation and routine inspection and testing protocols.

Overall remarks. Not withstanding the different requirements, aims and scope of the above documents, specific areas of risk management (including control measures) were identified as either not being addressed or lacking details in some or all of the documents[4]. In summary these are:

- safety requirements/precautions;
- restrictions/requirements (including incompatible materials) for retrofitting extinguishants with blends containing HCFC-123 blend;
- requirements for extinguishant disposal; and
- training requirements.

[3] In 1997, the FPIAA merged with the Australian Fire Protection Association to form the Fire Protection Association of Australia (FPAA). The FPAA is currently revising the FPIAA Code of Practice for the Design, Installation, Inspection and Testing of Gaseous Fire Extinguishants.

[4] It should be noted that these deficiencies were noted for future consideration by the relevant Australian Standards Committees, following the publication of PEC4.

14.2 Emergency procedures

For any hazardous chemical an emergency response plan is an essential component of occupational health and safety risk management. In the event of a substantial leak, spill, release or fire, a written procedure is necessary for workers and emergency services.

14.2.1 Refrigerant

Apart from guidelines for emergency discharge of refrigerants (ASHRAE, 1994), emergency procedures were not submitted for assessment. Key elements of an emergency plan should include:

- emergency shutdown procedures, displayed in a suitably conspicuous location;
- emergency contact number for the chiller maintenance company;
- respiratory protection (including self-contained breathing apparatus) in accordance with AS/NZS 1715 (Standards Australia, 1994b) and AS/NZS 1716 (Standards Australia, 1994c) and other personal protective equipment to be available and clearly labelled (AS 1319 (Standards Australia, 1994a)) at storage areas and outside equipment rooms;
- first aid procedures for acute health effects;
- an evacuation plan for building occupants; and
- clean-up procedures and waste disposal arrangements.

Clean-up and first aid procedures should be available on an MSDS (NOHSC, 1994b), which should be readily available to workers and emergency services. As HCFC-123 is not scheduled by the Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code) (Federal Office of Road Safety, 1998) there are no guidelines for accidental exposure during transportation.

14.2.2 Extinguishant

An emergency response plan was not submitted for assessment. Both NAF S-III and NAF P-III are regulated by the ADG Code (Federal Office of Road Safety, 1998) and a separate emergency response plan is required for transportation.

Transport and handling

The Hazchem emergency action code for NAF S-III specified by the label in AS/NZS 4214.5 (Standards Australia, 1995c) recommends the use of 'water fog' for dispersal/dilution of spillages together with the use of full protective clothing.

According to the ADG Code (Federal Office of Road Safety, 1998) the most appropriate emergency procedure guide for the two major ingredients (>90%) of HCFC Blend A (NAF S-III)[5] and the two major ingredients (>40%) of HCFC Blend C (NAF P-III)[6] is 2C2.

[5] HCFC-22 and HCFC-124.
[6] HFC-134a and HCFC-124.

Clean-up and first aid procedures should also be available on the MSDS (NOHSC, 1994b) which should be readily available to workers and emergency services.

Discharge, testing and filling of extinguishant systems

For fire situations suitable safeguards should be provided to ensure prompt evacuation from and prevent entry into hazardous atmospheres and also to provide the means for prompt rescue of any trapped personnel. Similarly an emergency response plan should cover accidental discharge during testing and filling procedures. The following elements should form the basis for appropriate action in response to discharge of HCFC-123 extinguishants:

- an evacuation plan for building occupants, for example, conducting fire drills;
- first aid procedures;
- respiratory protection,[7] including SCBA;
- emergency contact telephone numbers; and
- clean-up procedures.

Emergency procedures for professional firefighters are well developed and assessment of such is not within the scope of this report. Specific information on the hazards of HCFC-123 containing extinguishants should be made available to firefighters. In addition to the manufacturers' MSDS, current information on extinguishant hazards is available from the Commonwealth Fire Board (1994).

14.3 Hazard Communication

14.3.1 Education and training

Education and training form the basis for management of OHS risks. Guidelines for the induction and training of workers potentially exposed to hazardous substances are provided in the NOHSC *National Model Regulations and Code of Practice for the Control Workplace Hazardous Substances* (NOHSC, 1994c), which lists the key components of a good induction and training program. In addition, the ANZECC *Revised Strategy for Ozone Protection* (ANZECC, 1994) calls for training of all persons involved in the use of ozone-depleting substances. In particular, training should cover the health hazards associated with both acute and chronic exposure to HCFC-123, include instruction on the use of recommended personal protective equipment - particularly in the fitting and use of respirators - and provide information on clean-up and disposal.

14.3.2 Material Safety Data Sheets and labelling

Material Safety Data Sheets

MSDS are the primary source of information for workers employed in the handling, use, storage and disposal of hazardous chemicals and must be made available to all employees potentially exposed to HCFC-123 in the workplace in

[7] In accordance with Australian/New Zealand Standard AS/NZS 1715 and Australian/New Zealand Standard AS/NZS 1716.5.

accordance with the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

In 1996, 5 MSDS for HCFC-123 and 2 MSDS for blends containing HCFC-123 (extinguishants) were submitted for assessment and evaluated according to a prescribed set of criteria from a recognised study (PEC4, Section 14.3.2). Although the majority of the MSDS submitted for assessment were rated as 'adequate', none were considered 'nearly complete'. In 1998, 4 notifiers submitted MSDS for HCFC-123 and blends containing HCFC-123 (extinguishants) for the purposes of the secondary notification of HCFC-123. These MSDS were evaluated for availability and quality of data using the same criteria which were applied to the MSDS submitted in 1996. Scorings for individual MSDS evaluated in 1998 are presented in Table 12.

Table 12 - Evaluation of MSDS made available for assessment in 1998

MSDS	Company details (out of 5)	Identification (out of 28)	Health hazard information (out of 34)	Precautions for use (out of 16)	Safe handling and use (out of 12)	Total score (% of maximum)
A*	4	25	32	15	12	93
B*	5	26	25	11	12	82
C*	5	28	28	16	11	93
D†	4	25	25	10	9	77
E†	4	25	25	10	9	77

* *MSDS for HCFC-123 refrigerants*
† *MSDS for extinguishants containing HCFC-123 (HCFC Blends A and C)*

A qualitative assessment for the above total scores can be obtained for each MSDS using the following prescribed scale (Workcover, 1993):

Total score	Adequacy	Meaning
0-40%	Inadequate	Unacceptable. Should not be used
41-60%	Poor	Only to be used as an interim measure
61-80%	Good	Adequate
81-100%	Very good	Nearly complete/complete

Overall, MSDS had improved considerably since 1996, with 2 of 5 rated as 'adequate' and 3 as 'nearly complete'. However, only one MSDS identified HCFC-123 as hazardous according to the NOHSC *Approved Criteria for Classifying Hazardous Substances*. Moreover, only one MSDS had been updated with information about human liver effects from occupational exposure to HCFC- 123 and with data from new animal studies, such as the lactation study in rats.

An updated 'sample' MSDS for HCFC-123 refrigerant[8], prepared in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b) is provided at Appendix 1. This 'sample'

[8] Some of the information in this MSDS may also be appropriate for HCFC-123-containing extinguishant blends.

MSDS was compiled from the information contained in PEC4 and data made available for reassessment and is intended for guidance purposes only. Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), manufacturers and importers are responsible for preparing[9] MSDS and ensuring information is up-to-date.

Labels

In accordance with the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), all containers of hazardous substances supplied to, used in, or handled in the workplace should be appropriately labelled to allow that substance to be used safely.

For the purposes of the secondary notification of HCFC-123, 3 labels for HCFC-123 refrigerant and 2 labels for extinguishants containing HCFC-123 were submitted for assessment. These labels were assessed for requirements under the NOHSC *National Code of Practice for the Labelling of Workplace Hazardous Substances* (NOHSC, 1994a). The assessment took the form of a qualitative appraisal with respect to the inclusion of the following categories of information:

- substance identification;
- hazard category/signal word;
- ADG Code classification (Federal Office of Road Safety, 1998);
- risk information (or phrase);
- safety information (or phrase);
- first aid information (or phrase);
- information on spills/leaks; and
- firefighting precautions.

Only one of the labels for HCFC-123 (refrigerant) included the signal word 'Hazardous' and one label provided no information at all on risk, first aid and spills and leaks.

NAF S-III cylinder and NAF P-III fire extinguisher labels meet the requirements of the relevant Australian Standards (AS/NZS 4215.5 (Standards Australia, 1995c) and AS/NZS 1841.1 (Standards Australia, 1997a). The NAF S-III label for cylinders used in fixed fire control systems also includes most of the information required under the NOHSC *National Code of Practice for the Labelling of Workplace Hazardous Substances* (NOHSC, 1994a). However, the label used on NAF P-III portable fire extinguishers provides no information at all about substance identification, hazard category, risk, safety precautions or first aid.

[9] It is recommended that the preparation of an MSDS is carried out by a suitably informed and qualified person.

14.4 Exposure standards

14.4.1 Atmospheric monitoring

Air monitoring is necessary to obtain a quantitative estimate of exposure for the purpose of determining the effectiveness of control measures. Continuous monitoring of workroom air at chiller installations, using an automated detection system, is recommended by Australian/New Zealand Standard AS/NZS 1677 (Standards Australia, 1998) and ASHRAE Standard 15 (ASHRAE, 1994) and is currently reported to be standard practice for HCFC-123. Detection systems are usually adjusted to activate both an alarm and mechanical ventilation at pre-set trigger concentrations.

This type of monitoring not only provides an instant warning of excursions above a set airborne level of HCFC-123 but also provides a continuous record of TWA exposure levels for each working day. The main problem with this type of monitoring system is lack of specificity, as other chlorinated compounds (including CFC-11) have been known to interfere with detection, particularly at low exposure levels, that is, less than10 ppm.

It is important to ensure that the positioning of detectors is appropriate for assessing actual worker exposures encountered during maintenance operations. Therefore, detectors should be located in areas where refrigerant vapour leaks are most likely and should be positioned to account for air flow patterns in the equipment room. There exists a need for routine personal monitoring to validate the accuracy of automated monitors and the siting of detectors.

The usefulness of routine monitoring during maintenance/installation of systems using HCFC blend extinguishants is difficult to evaluate as exposures (levels and duration) have not been characterised.

14.4.2 Regulatory standards

Following the publication of PEC4 in 1996, a draft standard for HCFC-123 was released for public comment by the NOHSC Exposure Standards Expert Working Group in 1997. The draft proposed a TWA exposure standard of 10 ppm and the assignment of carcinogen category 3 to HCFC-123. The draft standard has not been reviewed by NOHSC as the exposure standards programme is currently undergoing a major revision, which is expected to be completed in 1999.

Overseas, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has classified HCFC-123 as a group IIIB carcinogen and therefore a maximum workplace concentration (MAK value) was not established (Deutsche Forschungsgemeinschaft, 1994). More recently, the Workplace Environmental Exposure Level (WEEL) Committee of the American Industrial Hygiene Association has recommended a limit of 50 ppm (8-h TWA) for occupational exposure to HCFC-123 (AIHA, 1998).

For HCFC-123 in fire extinguishants, the US National Research Council and National Academy of Sciences have recommended that the US Air Force adapt a 1-min emergency exposure guidance level of 1900 ppm HCFC-123. This level is derived from the EC_{50} for cardiac sensitisation in dogs determined by

Trochimowicz & Mullin (1973) divided by an uncertainty factor of 10 for interspecies variability (National Academy of Sciences, 1996).

14.4.3 Industry-set exposure limits

Refrigerant

In June 1991, following the publication of preliminary findings from the PAFT chronic oncogenicity/toxicity study, the industry set AEL-TWA for HCFC-123 in workroom air was reduced, at the recommendation of Du Pont, from 100 ppm to 10 ppm. In September 1993 following publication of the final study report from PAFT together with results from a follow-up metabolism/mechanistic study, Du Pont (1993) increased the AEL-TWA from 10 ppm (62.5 mg/m^3) to 30 ppm (187 mg/m^3). HCFC-123 was reviewed again in 1997. Based on the results of additional mechanistic studies and new developmental/lactional studies in rats and monkeys, Du Pont concluded that an AEL of 50 ppm should provide an adequate margin of safety for workers and increased the AEL for HCFC-123 from 30 to 50 ppm (8- and 12-h TWA).

In April 1998, AlliedSignal Inc. lowered its recommended permissible exposure level from 50 ppm to 10 ppm HCFC-123 (8-h TWA). This was prompted by the occurrence of 8 cases of liver disease associated with occupational exposure to the vapours of solvent degreasers containing 97.5-100% HCFC-123 (see Section 11.3 above). AlliedSignal Inc. also withdrew the solvent degreasers from the market.

Elf Atochem (Australia) Pty Ltd recommends that workplace exposure to HCFC-123 be kept below 10 ppm (TWA) (Elf Atochem, 1998).

Other industry-set workplace exposure levels for HCFC-123 include an Emergency Exposure Limit (EEL), currently set at 1000 ppm with a ceiling limit of 2500 ppm. The EEL is defined as the maximum concentration to which a worker can be exposed for a 1-h period, with a 1-min ceiling limit in the event of an emergency such as a spill.

Extinguishant

There are no industry-set exposure limits for atmospheric levels of HCFC-123 arising from the use of HCFC-blend fire extinguishants. However, according to Australian/New Zealand Standard AS/NZS 4214.5 as amended in July 1997 (Standards Australia, 1995c), NAF S-III total flooding systems shall not be used in concentrations greater than the NOAEL in normally occupied areas unless fitted with a lock-off valve and provided with means to ensure safe egress of personnel within 30 seconds prior to the discharge of extinguishment. The Standard quotes a NOAEL of 10.0% by volume, which is claimed to be based on health-based studies, although these were not cited in the Standard and were unavailable for assessment. Such a concentration of extinguishant would lead to an exposure of approximately 0.5% HCFC-123 (2900 ppm HCFC-123).

14.5 Health surveillance

There are no formal requirements for health surveillance programs for workers exposed to HCFC-123. HCFC-123 is not listed on the NOHSC Schedule of

Substances Requiring Health Surveillance (Schedule 3) in the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

In accordance with the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), employers have a responsibility to provide health surveillance in those workplaces where the workplace assessment has shown that exposure to a hazardous substance may lead to an identifiable substance-related disease or adverse health effect.

Since the publication of PEC4, reversible liver effects have been reported in humans following repeated exposure to HCFC-123 at levels ranging from 5-500 ppm. In some cases the effects were limited to elevated AST and ALT levels and were not associated with manifest clinical illness. Further research is needed to establish whether similar findings can be demonstrated in chiller technicians. In the affirmative, routine atmospheric monitoring might not be sufficient to evaluate exposure to HCFC-123 to chiller technicians and routine health surveillance could be indicated.

The risk assessment for HCFC-123 indicates that under 'anticipated conditions' of use, risks of adverse health effects for workers involved in firefighting are likely to be low. Therefore, for this population routine health surveillance is not indicated at present.

15. Environmental Risk Assessment

15.1 Environmental fate

15.1.1 Aquatic fate

Significant amounts of HCFC-123 are not expected to enter aquatic environments because of limited solubility and high volatility. Spills to water would largely evaporate as HCFC-123 is not readily biodegradable. Oxygen consumption during a 28-day closed bottle test (OECD guideline No. 301D) amounted to 24% of theoretical at a concentration of 12.5 mg/L. The test substance also proved resistant to chemical degradation, with chemical oxygen demand (acid dichromate at 150ºC for 2 h) being only 14% and 4% of theoretical at concentrations of 243 and 567 mg/L, respectively (Jenkins, 1992a).

Like other halogenated solvents, HCFC-123 has the potential to contaminate groundwater. However, HCFC-123 is reluctant to dissolve, notwithstanding moderate solubility, and degases readily from solution even at concentrations well below the solubility limit, as was evident in aquatic toxicity testing (see below). Furthermore, the isomer HCFC-123a has been shown to undergo reductive dechlorination under the influence of bacteria in methanogenic landfill leachate (Lesage et al., 1992). Thus anaerobic biodegradation pathways should exist for HCFC-123, although they are unlikely to represent a significant degradation mechanism because of limited exposure of anaerobic environments to the volatile halocarbon.

While HCFC-123 itself is expected to be mainly associated with the atmosphere, hydrophilic substances which precipitate in rain, such as TFA, are formed from its degradation. No biodegradation was observed when the sodium salt of TFA was subjected to the closed bottle test (OECD guideline No. 301D) even though the test was continued for 77 days (Van Ginkel & Stroo, 1993). While biodegradation was not observed in these laboratory tests, recent studies (Visscher et al., 1994) demonstrate that trace amounts of TFA can be degraded by reductive defluorination under anoxic conditions and by decarboxylation under oxic conditions, implying that significant microbial sinks exist in nature for the elimination of TFA from the environment. However, the rate and significance of these processes remain uncertain.

TFA will be deposited on both land and water, but is expected to become associated mainly with the aquatic compartment as the sodium salt underwent minimal sorption (average 0% from duplicate tests using OECD guideline No. 106 in three different soils (Van Dijk, 1992)).

15.1.2 Atmospheric fate

Because of its volatility, any HCFC-123 released to the environment will partition almost entirely to the atmosphere, where its main mode of degradation

will be reaction with tropospheric hydroxyl radicals. It has been estimated that 88% of emissions will be so degraded (Prinn & Golombek, 1990), leading to an estimated atmospheric lifetime at steady state of 1.4 years (WMO, 1995). This compares with 50 years for CFC-11 (WMO, 1995).

Mechanistic studies (Atkinson et al., 1993) on hydrogen abstraction from HCFC-123 used chlorine rather than hydroxyl radicals because of their greater ease of laboratory generation. The only product detected, in 98% yield, was trifluoroacetyl chloride. A minor component was thought to be chlorodifluoroacetyl fluoride, formed from the isomer HCFC-123a. Following hydrogen abstraction, the pentahaloalkyl radical reacts with atmospheric oxygen to form the peroxyalkyl radical, which reacts further to the corresponding alkoxy radical. Chlorine elimination generates trifluoroacetyl chloride.

Trifluoroacetyl chloride is expected to be removed from the troposphere by dissolution in cloud water, hydrolysis to TFA and precipitation in rain. Alternatively, further photolysis in the upper troposphere leads to carbonyl fluoride, which can photolyse further to hydrogen fluoride in the stratosphere. Model simulations (Hayman & Johnson, 1992) indicate that formation and precipitation of TFA is the dominant removal mechanism, although photolysis to carbonyl fluoride in the upper troposphere is also significant.

Trifluoroacetyl chloride may also be transported to the stratosphere under turbulent conditions. Its behaviour in the stratosphere will be similar to that for carbonyl halides, being removed mainly by photolysis. However, the available evidence (Mellor et al., 1993) suggests that the formation of fully halogenated substances, such as CFC-11, from photolysis of triflouracetyl chloride is sufficiently low that the ODP of the parent compound, HCFC-123, will be increased by less than 0.01.

Carbonyl fluoride does not react with hydroxyl radicals or undergo photochemical transformation at significant rates in the troposphere. Its fate is somewhat speculative as its Henry's law solubility and reactive sticking coefficient (a measure of the reaction probability on aqueous surfaces) are unknown. However, by using data for phosgene, a tropospheric lifetime of 17 days may be estimated for carbonyl fluoride with respect to incorporation and hydrolysis in clouds (Kanakidou et al., 1992). Dry deposition may also be important. Tropospheric loss mechanisms may be inferred from the observation of carbonyl fluoride in the stratosphere, but not in the troposphere (Helas & Wilson, 1992). However, such conclusions are tentative as stratospheric sources of carbonyl fluoride include the common CFCs, CFC-11 and CFC-12.

15.1.3 Biomolecular fate

The metabolic transformation of TFA has been demonstrated in selected aquatic organisms spanning a range of trophic levels (Standley & Bott, 1998).

When testing for aquatic bacterial incorporation of TFA, microbial communities collected periodically from mesocosms receiving long-term (2.5 years) exposure to TFA showed a trend towards increasing incorporation over the study period. This suggested either a slow increase in the ability of the cultured microbial community to metabolise TFA or a shift in population towards species with a greater ability to incorporate TFA.

Aquatic plant and animal macroorganisms were also tested, and incorporation of radiolabelled TFA by aquatic organisms exposed in microcosms was shown to be taxon dependent, with oligochaetes (worms) and jewelweed containing the most chemical. Within these organisms, the radiolabel was found in large quantities within lipid and protein, indicating the organisms were metabolising it through the use of TFA as an intermediate in the synthesis of lipid and acetylated proteins. Therefore, uptake appeared to be dependent on specific metabolic and trophic transfer pathways. No substantial biological effects were found.

15.2 Environmental Effects

15.2.1 Aquatic organisms

HCFC-123 appears to be slightly toxic to practically non-toxic to fish. No mortality occurred in fathead minnows exposed for 96 h to solutions of HCFC-123 (350 mg/L nominal, 76 mg/L measured, isomeric ratio 4:1 from inspection of HRGC chromatograms) in a flow-through system. Fish were anaesthetised by exposure to HCFC-123, becoming immobilised within minutes on static exposure to 700 mg/L (nominal) but regaining full activity some 12-14 h later as the halocarbon degassed from solution. However, when fish were maintained in the stock solution at this same nominal concentration for 6 h, recovery did not occur and all fish died. Concentrations to which fish were exposed are unclear as solubility in the diluter stock reservoir was visibly incomplete, and HCFC-123 degassed readily from test solutions, despite the nominal concentrations being well within the stated solubility limit (Pierson, 1990a).

The effects of HCFC-123 on rainbow trout were investigated under semi-static conditions, with test media renewed at 24-h intervals. Measured concentrations were close to nominal except for the highest concentration tested of 133 mg/L in which dissolution was visibly incomplete and the mean measured concentration was 68% of nominal. All fish died within 24 h at this concentration. Results are expressed as mean measured concentrations. A no-effect concentration could not be obtained as fish exhibited lethargic behaviour and darkened pigmentation even at the lowest concentration of 15 mg/L (Jenkins, 1992b).

The first of the two cladoceran tests used static conditions, with endpoints expressed as mean measured concentrations, which were significantly lower than nominal at test initiation but increased during the test (Jenkins, 1992c). Measured concentrations were consistently 25% or less of nominal in the second static test on Daphnia magna. Anaesthetic effects were again observed (Pierson, 1990b). Results in both tests are indicative of slight toxicity.

An algal growth inhibition test was conducted in sealed vessels under static conditions with concentrations measured at 0, 48 and 96 h. As in the other tests, HCFC-123 proved reluctant to dissolve, and measured concentrations increased during the first 48 h due to slow dissolution and then declined because of volatilisation. The EC_{50} (67.8 mg/L) based on biomass and mean measured concentrations indicates HCFC-123 to be slightly toxic to algae (Jenkins, 1992d).

Results of the studies in aquatic organisms are summarised in Table 13.

Table 13 - Summary of effects of HCFC-123 in aquatic organisms

Test	*Species*	*Results*	*Reference*
Acute toxicity (96 h)	Fathead minnow	LC_{50} > 350 mg/L	Pierson, 1990a
Acute toxicity (96 h)	Rainbow trout	LC_{50} = 55 mg/L	Jenkins, 1992b
Immobilisation (48 h)	*Daphnia magna*	EC_{50} = 17.3 mg/L	Jenkins, 1992c
Immobilisation (48 h)	*Daphnia magna*	EC_{50} = 45.8 mg/L	Pierson, 1990b
Algal growth inhibition (96 h)	*Selenastrum capricornutum*	EC_{50} = 67.8 mg/L	Jenkins, 1992d

Chronic effects on aquatic organisms would not be expected as HCFC-123 is clearly non-persistent in water, even at concentrations below the solubility limit.

15.2.2 Atmospheric effects

Halocarbon refrigerants can affect the atmosphere. The dominant concern associated with chlorine or bromine containing refrigerants and extinguishants is that they can transport these halogens to the stratosphere where they catalyse the destruction of ozone.

Because of their high tropospheric stability, fully halogenated CFC refrigerants have been phased out in favour of HCFC refrigerants as an interim measure while ozone benign replacements, for example, HFCs, are developed. HCFC-123 is one of these transitional refrigerants. Model calculations (Fisher et al., 1990a) indicate that the ozone depletion potential (ODP) of HCFC-123 is around 2% of that for CFC-11 and CFC-12, which have ODPs of about 1. Numerous studies confirm these findings.

Whereas HCFC-123 is removed predominantly in the troposphere, there is some degradation and release of chlorine in the stratosphere by reaction with hydroxyl radicals and photolysis. Computer modelling studies undertaken to date indicate that only 1-2% of HCFC-123 would reach the stratosphere. While further research in this area may be forthcoming, and should be monitored, it appears unlikely that the ozone depletion potential of HCFC-123 will alter significantly from the currently estimated value (0.02 relative to CFC-11).

Like other halocarbons, HCFC-123 contributes to the global warming potential (GWP) of the atmosphere. However, its atmospheric lifetime is short at less than 2 years, and its GWP is only 2% of that for CFC-11 and less than 1% of that for CFC-12 (Fisher et al., 1990b). CFC-11 has the shortest lifetime and lowest GWP of the common CFCs. Numerous studies confirm these findings.

15.3 Hazard evaluation

HCFC-123 does not represent a direct ecotoxicological hazard as both exposure and toxicity are low. Data on HCFC-123 and other HCFCs that have been reviewed by the US EPA generally support the contention that these chemicals exhibit a low level of ecotoxicity. However, HCFC-123 may exhibit biological effects indirectly by impacting on the atmosphere, particularly stratospheric ozone. The stratospheric ozone layer reduces the amount of harmful ultraviolet radiation that reaches the Earth's surface. While the ODP is reduced by a factor of 50 relative to CFC-11, it remains finite. Accordingly, HCFC-123 is only

considered acceptable for use in refrigeration equipment as an interim replacement for fully halogenated CFCs.

Similarly, the use of blends containing HCFC-123 in the fire protection industry (to replace Halons 1211 and 1301) is only considered acceptable as an interim measure pending development of ozone benign alternatives. However, the interim transition represents a major hazard reduction, as Halons 1211 and 1301 have ODPs of 5 and 12-13 respectively (WMO, 1995). In addition atmospheric lifetimes are approximately 20 and 65 years respectively (WMO, 1995).

Greenhouse concerns are less significant than ODP concerns for halons because of the relatively short atmospheric lifetimes. However, some easing of GWP can be expected from the transition to the HCFC blends in view of the shorter lifetimes of their component gases of:

- HCFC-123 - 1.4 years;
- HCFC-124 - 5.9 years;
- HCFC-22 - 13.3 years; and
- HFC-134a - 14.0 years (WMO, 1995).

Due to its low Henry's law constant it may be predicted that TFA formed in the atmosphere will partition in the various aqueous environmental phases. Consequently, TFA was detected and measured in fog, rain, snow and surface waters obtained in 1994-96 from several locations in California and Nevada (Wujcik et al., 1998). Fog and rain samples contained 0.031-3.78 µg/L TFA. Snow samples taken in more remote areas contained 0.051-0.584 µg/L TFA. Surface water concentrations of TFA varied from 0.055 to 40.5 µg/L depending on type and location, although the highest reading was an order of magnitude greater than the next highest measurement. The authors suggested that the magnitude of TFA levels indicated that the formation from HCFC and HFC degradation is occurring more rapidly than expected, or that alternative sources of TFA exist.

It has been estimated recently that by the year 2010 the global average TFA concentration in rainwater will be 0.160 µg/L, 15% of which will be due to atmospheric degradation of HCFC-123, the other 85% due to degradation of HCFC-124 and HFC-134a. This level of TFA is three orders of magnitude below toxic thresholds of the most sensitive species yet addressed. However, under high evaporation conditions TFA levels in some wetlands could reach 100 µg/L within a few decades, assuming no loss by degradation or water seepage (Schwarzbach, 1995; Tromp et al., 1995). TFA is known to inhibit plant growth in the range of 10^2-10^6 µg/L (Wujcik et al., 1998). While there is no immediate prospect of such levels being reached in Australia, further research in this area should continue to be monitored.

15.4 Risk management

Adherence to the *Australian Refrigeration and Air Conditioning Code of Good Practice* (AFCAM, 1997) is expected to minimise environmental emissions of HCFC-123 arising from current use, handling and disposal of refrigerant. Australia's ratification of the Copenhagen amendment to the Montreal Protocol will require that current uses of HCFCs are controlled prior to phase-out (EPA, 1995).

Extinguishant use entails inevitable atmospheric release. However, State legislation prohibits discharge of halons from firefighting systems during testing and training, and similar measures are expected with respect to HCFCs. Adherence to the Fire Protection Industry Association's *Code of Practice for Design, Installation, Inspection and Testing of Gaseous Fire Extinguishants* (FPIAA, 1995) is expected to minimise environmental emissions of HCFC-123 arising from extinguishant testing.

To ensure an orderly phase out, the Commonwealth proposes controls on the importation and manufacture of HCFCs at a level that will meet the needs of existing owners of HCFC-based equipment, but will not encourage the use of HCFCs where alternative technologies are available. The controls will be administered under the *Ozone Protection Act 1989* (Cwlth). Two yearly licences to import and manufacture HCFCs will be issued and an administrative fee of $10,000 will be charged. In addition, an activity fee of $2000 per ODP tonne of HCFCs imported or manufactured will be placed in a trust fund to be created which will be used to improve public awareness of the phase-out and alternatives.

An Australian phase-out timetable for HCFCs from 1996 to 2030 has been proposed. The phase out will discriminate against consumption of those HCFCs which contribute most to ozone depletion by imposing an activity fee based on the ozone depletion potential of individual HCFCs.

The proposed phase-out timetable meets Australia's current obligations under the Montreal Protocol and will be responsive to future changes to the Protocol. Regulations will gradually reduce the quantity of HCFCs imported and manufactured until 2015 with a small quantity available for the maintenance of long-life commercial air conditioning equipment until 2030.

If total consumption does not exceed annual targets set by the Commonwealth Minister for the Environment, industry may be allowed to self-regulate. Annual targets will be set at least 2 years ahead by regulations. Industry believes that the proposed Australian phase-out timetable is realistic and has hailed the scheme as innovative.

This policy was endorsed in its entirety by Commonwealth Cabinet on 24 October 1994. Amendments to the *Ozone Protection Act (1989)* were passed by Parliament in October 1995.

The policy for control of HCFC emissions in Australia proposes the extension of some existing controls on CFCs and halons to include the control of future emissions of HCFCs. States and Territories recommend that:

- the sale of HCFCs should be restricted to registered persons;
- service personnel for HCFC equipment need to have some formal training in reducing emissions of HCFCs;
- service personnel should work in accordance with appropriate codes of practice;
- unnecessary emissions of HCFCs should be banned;
- sales of HCFCs should be recorded and reported; and
- controls should be reviewed in 2000.

The proposed controls substantially exceed Australia's international obligations but industry agrees that they provide sufficient HCFCs to meet Australia's current and future needs in a regulatory framework that discourages new or unnecessary uses of HCFCs.

Although non-government organisations prefer that HCFCs not be used at all, they recognise that existing equipment has to be phased out without delaying the transition away from CFCs. Government environment departments, industry and non-government organisations are keen to ensure that current emission controls on CFCs and halons are extended to HCFCs.

Ozone-depleting refrigerants must not be released to the atmosphere. Under Commonwealth legislation manufacturers or importers of HCFC-123 are required to accept recovered HCFC-123 and be responsible for its storage, recycling or destruction. A number of initiatives have been implemented to assist in the recycling of CFCs and halons in Australia such as the establishment of the Halon Bank under DASCEM Holdings Pty Ltd.

16. Summary and Conclusions

In Australia, HCFC-123 is currently being used as a replacement for CFC refrigerants (in industrial systems) in the air-conditioning industry and in HCFC blends as replacements (in both portable and fixed extinguisher systems) for halons in the fire protection industry. Trace amounts are used for calibration of alarms or detectors used in refrigeration plants. As with CFCs, HCFCs are being phased out under the *Ozone Protection Act 1989* due to their ozone-depleting potential.

The main sources of occupational and environmental exposure to HCFC-123 in Australia are release during chiller maintenance and firefighting.

New data on kinetics and metabolism, animal toxicity and human health effects from repeated HCFC-123 exposure have prompted a partial revision of the human health hazard classification and risk characterisation as assessed in PEC4.

Acute effects from inhalation of HCFC-123 are CNS depression, cardiac sensitisation and asphyxiation and possible liver damage. In animals, the most sensitive acute effect is hepatotoxicity which was seen in guinea pigs at 1000 ppm, the lowest dose tested. Data on structural analogues indicate that humans are likely to be less sensitive than guinea pigs with respect to acute liver toxicity, although this inference should be regarded as tenuous in light of recent reports which indicate that humans are more sensitive than experimental animals to short-term repeated exposure to HCFC-123.

Occupational exposure to acutely toxic levels of HCFC-123 would not be expected for chiller maintenance workers, as monitoring data indicate that peak levels do not usually exceed a few hundred parts per million.

Levels of HCFC-123 (in the breathing zone) have been measured around 1000 ppm from indoor discharge of portable fire extinguishers. Although such a level of exposure is unlikely to present a health risk, exposure to other HCFC ingredients will increase the risk.

Acute health risks for professional firefighters are low due to deployment of personal protective equipment, however, the risk of acute effects may be significant for other workers using portable extinguishers, particularly where discharge takes place in confined work areas. Although NAF S-III has been shown to be a mild cardiac sensitising agent in dogs at a concentration of 12%, occupational exposure to extinguishant from fixed (total flooding) systems is not expected to occur under normal discharge conditions. Additional health risks may arise from exposure to toxic substances (including phosgene and hydrogen fluoride) formed from both extinguishant combustion and reaction of extinguishant with other products of combustion.

Chronic effects from inhalation of HCFC-123 are liver injury and possible damage to pancreas and testes, including a potential carcinogenic hazard in all three organs. Although humans may develop biochemical signs of liver injury such as elevated AST and ALT at exposure levels below 50 ppm HCFC-123, animal studies point to a NOAEL for chronic effects on liver, pancreas and testes

of 100 ppm HCFC-123. Furthermore, the available mechanistic and genotoxicity data indicate that this concentration is below the threshold for tumour induction by HCFC-123.

HCFC-123 metabolites in breast-milk of exposed women may present a health risk to breast-fed infants, as the major metabolite TFA is excreted in breast-milk of monkeys and rats and retarded growth of rat pups has been determined to be a lactational effect with a maternal LOAEL of 30 ppm.

Although it has been demonstrated that compliance with existing control measures as described in the relevant codes and standards for the air-conditioning industry results in TWA HCFC-123 (airborne) exposure levels of less than 5 ppm and generally less than 1 ppm, peak levels in excess of 100 ppm may be encountered during certain maintenance operations. Reversible liver effects have been reported in humans following repeated exposure (by inhalation) to HCFC-123 at levels ranging from 5-500 ppm. In some cases the effects were limited to elevated levels of liver enzymes in the blood and not associated with manifest clinical illness. Further research is needed to establish whether similar effects can be demonstrated in chiller technicians who are potentially exposed on a routine basis to levels (airborne) of HCFC-123 that may exceed the lower end of this range of exposures.

Chronic exposure to HCFC-123 extinguishant blends is likely to be minimal due to: (a) deployment of personal protective equipment by professional firefighters; and (b) the infrequency of exposure to extinguishant discharges for other worker populations, and hence the risk of chronic effects is also likely to be negligible.

The content of HCFC-123 in calibration gas (around 20 or 60 mg per cylinder) is considered too low to pose any occupational health risks during alarm calibration activities.

In general, the codes and standards reviewed for both refrigerants and extinguishants provided sufficient information on engineering controls but lacked details in areas such as information about health effects and safety requirements/precautions. Labels and MSDS generally met National Commission requirements, although only one importer classified HCFC-123 as hazardous according to the NOHSC Approved Criteria (NOHSC, 1998). Only one MSDS had been updated with information about human liver effects from occupational exposure to HCFC-123 and with data from new animal studies, such as the lactation study in rats. One refrigerant label contained no information on risk, first aid or spills and leaks. The label used on NAF P-III portable fire extinguishers (60% HCFC-123) provided no information about substance identification, hazard category, risk, safety precautions or first aid.

Based on the use pattern of HCFC-123, it is considered that the notified chemical will not pose a significant hazard to public health. If the conditions of use are varied, greater exposure of the public to the chemical may occur. Under such circumstances, further information may be requested to assess the hazards to public health.

HCFC-123 is not directly toxic to flora and fauna. Indirect biological effects are possible due to the contribution of HCFC-123, albeit small, to ozone depletion. A possibility exists that the degradation product TFA may accumulate within a few decades to potentially toxic levels in certain wetlands. Recent findings suggest

that TFA degrades in aerobic and anaerobic environments, but further research on this aspect should be monitored.

17. Recommendations from Secondary Notification Assessment

17.1 New recommendations

The main concern arising from the secondary notification of HCFC-123 is the emergence of substantial evidence that repeated occupational exposure to HCFC-123 may cause adverse liver effects in humans. Furthermore, it has been demonstrated that the main metabolite of HCFC-123, TFA, is excreted in milk of rats and monkeys and that reduced growth rate in rat pups is a lactational effect.

The recommendations arising from a critical review of the health effects data that has become available since the publication of PEC4 are, as follows:

- Based on case reports relating to liver effects in humans, HCFC-123 should be classified with risk phrase R48/20 – Harmful: danger of serious damage to health by prolonged exposure through inhalation.
- Based on the demonstration that TFA is excreted in the milk of rats and monkeys and that reduced pup growth in rat pups is a lactational effect, HCFC-123 should be classified with risk phrase R64 – May cause harm to breast-fed babies.
- Priority should be given to the development of a national exposure standard which takes into account the occurrence of liver effects in humans following repeated exposure to HCFC-123 at air levels ranging from 5-500 ppm and also considers the maternal LOAEL for reduced pup growth in rats (determined at 30 ppm).
- Because of the hepatotoxicity and high vapour pressure of HCFC-123, the chemical should not be used as a solvent degreaser or in other industrial applications which may lead to excessive workplace exposure to the chemical. Likewise, HCFC-123 should not be used as a refrigerant in systems where there is a risk of leakage into confined, occupied spaces, such as in vehicle air-conditioning systems.
- A new study of the cardiac sensitisation potential of the extinguishant blend NAF S-III (4.75% HCFC-123) failed to determine a NOAEL and should not be used as guidance for a health-based design concentration for fixed fire control systems employing NAF S-III as flooding agent.
- A biological monitoring study should be carried out to establish whether sub-clinical liver effects (elevated levels of circulating liver enzymes without manifest clinical illness) occur in chiller maintenance technicians who are subject to repeated exposure to low levels of HCFC-123. In the affirmative, consideration should be given to routine health surveillance of chiller workers exposed to the chemical.

17.2 Recommendations carried over from PEC4

New data have become available about the possible mechanisms for the induction of tumours by HCFC-123 in the 2-year bioassay in rats, mainly with regard to the biological effects of peroxisome proliferators and the effects of HCFC-123 on the hypothalamic-pituitary-gonadal endocrine system in rats. A global assessment of the available data indicates that the mechanisms of tumour induction for HCFC-123 include the activation of a nuclear hormone receptor that is responsive to peroxisome proliferators; hepatocellular damage, necrosis and regenerative proliferation; hepatic cholestasis; and interference with the hypothalamic-pituitary-testicular axis. Of these mechanisms, only hepatocyte growth induction by peroxisome proliferators and fluctuations in male prolactin levels are considered likely to be irrelevant to humans. Therefore, it is recommended that HCFC-123 continues to be classified as a Category 3(b) carcinogen. The classification implies that further studies are necessary to reach a final decision on the carcinogenic status of the chemical. Such studies should include a carcinogenicity study in an animal species which is less susceptible to peroxisome proliferators than the rat as well as investigations of the effects of HCFC-123 on the expression of CCK in rats and on pituitary and gonadal sex hormone levels in primates.

Although MSDS and labels for HCFC-123 and HCFC-123 containing fire extinguishants have improved, most MSDS provide incomplete information about human health effects and animal toxicity data and all labels will need to be updated with risk and safety phrases that are consistent with the revised hazard classification of HCFC-123.

Industry data indicate that there has been a marked increase in the use of the HCFC-123 blend NAF P-III in portable fire extinguishers, with imports of NAF P-III (60% HCFC-123) up from 1 t in 1993-94 to 41 t in 1996-97. NAF P-III portable fire extinguishers are not available for domestic use, but may be used by workers who are not professional firefighters. The label provided by the largest distributor meets the requirements of the relevant standards (AS/NZS 1841.1 and 1841.7), but provides no information about substance identification, hazard category, risk, safety precautions and first aid. It is therefore considered appropriate to reiterate the recommendation that labels for portable fire extinguishers follow the requirements of the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994a).

Several industry codes of practice and Australian standards relating to refrigerating systems and gaseous fire extinguishants have been revised since the publication of PEC4 in 1996. Overall, these revisions have paid little attention to the relevant recommendations in PEC4. It remains appropriate to recommend that such codes and standards provide more information on occupational health and safety in general and on the health effects of repeated exposure to HCFC-123 in particular.

Given the increase in imports of HCFC-123 it is considered appropriate to strengthen the call for the Federal Office of Road Safety's Advisory Committee for the Transport of Dangerous Goods to classify HCFC-123 as a Class 9 Dangerous Good in view of its ozone-depleting potential, potential acute and chronic health effects and the toxic pyrolysis products of the chemical.

17.3 Consolidation of recommendations

Section 18 contains a consolidation of the recommendations arising from the primary assessment (PEC4) with those arising from this secondary notification.

18. Consolidated Recommendations

18.1 Classification

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1998), HCFC-123 is considered to be a 'Hazardous' substance.

With respect to the available health effects data and in accordance with the health effects criteria detailed in the Approved Criteria, HCFC-123 should be classified as:

- CARCINOGEN – CATEGORY 3;
- HARMFUL TO HEALTH BY PROLONGED EXPOSURE; and
- HARMFUL TO BREAST-FED BABIES

As a Category 3 carcinogen HCFC-123 falls into sub-category 3(b), signifying that further studies are necessary before a final decision on carcinogenic status can be made.

Products or preparations containing ≥1% by weight HCFC-123 should also be classified as 'Hazardous' or 'Harmful'. However, products containing other hazardous chemicals (for example, fire extinguishant blends) should be classified by taking into account the health effects of all ingredients.

18.2 Provision of information

As HCFC-123 is a hazardous substance, employers and suppliers should be aware of their obligations to provide information about the hazards of the chemical, such as MSDS and labels. Details of these obligations, consistent with employers' general duty of care, are provided in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

18.2.1 Material Safety Data Sheets

The NOHSC National Code of Practice for the Preparation of Material Safety Data Sheets (NOHSC, 1994b) provides guidance for the preparation of MSDS.

A survey of current MSDS for HCFC-123 and HCFC-123 containing extinguishant products showed that the following important items were omitted in some of the MSDS:

- a 'statement of hazardous nature', that is, the hazard classification according to the Approved Criteria or the word 'hazardous';
- information on potential human health effects from repeated exposure to HCFC-123.

- up-to-date summaries of all available animal data, including species, route of exposure and exposure levels;
- summary of the health effects of potential pyrolysis products of HCFC-123 containing extinguishants;
- information on the use and disposal of the substance, including any restrictions according to the *Ozone Protection Act (1989)*; and
- the current status of the Australian exposure standard, ADG Code classification and SUSDP scheduling and details of relevant Australian standards and codes.

It is recommended that manufacturers and importers review and upgrade the MSDS in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b) and ensure that the above items are included. A 'sample' MSDS for HCFC-123 refrigerant is provided at Appendix 1 for guidance.

18.2.2 Labels

The NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994a) provides guidance for the labelling of workplace hazardous substances.

It is recommended that labels be reviewed and upgraded to include risk and safety phrases, first aid procedures, emergency procedures and conform to disclosure requirements – that is, HCFC-123 is a 'Type I' hazardous ingredient and as such should be disclosed on the label when present in a mixture at ≥1% w/w. Consistent with its classification, the following risk and safety phrases are recommended for HCFC-123:

Risk phrases

R40	Harmful: possible risk of irreversible effects
R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation
R64	May cause harm to breast-fed babies

Safety phrases

S3/9	Keep in a cool, ventilated place
S23	Do not breathe vapour
S38	In case of insufficient ventilation, wear suitable respiratory equipment
S41	In the case of fire and/or explosion, do not breathe fumes

design elementHCFC-blend extinguishants containing other hazardous ingredients should be classified and labelled accordingly. Risk phrases R40 and R64 will apply to extinguishant blends (whether liquid or gaseous) containing ≥1% w/w HCFC-
123. Risk phrase R48/20 will apply to gaseous blends containing ≥5% w/w HCFC-123 and to liquid blends containing ≥10% w/w HCFC-123. Appropriate

safety phrases for blends should be selected from the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (1994a).

Given the increase in the importation of NAF P-III (60% HCFC-123), it is considered particularly important that labels for portable fire extinguishers containing HCFC-123 take into account the above requirements. They should also contain a prominent warning about using the extinguisher in a confined space.

18.2.3 Training and education

Guidelines for the induction and training of workers potentially exposed to hazardous substances are provided in the NOHSC *National Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

Workers potentially exposed to HCFC-123 need to be trained in safe work practices to be followed in the handling, storage, transportation and disposal of the chemical.

For chiller maintenance technicians, training provided at induction should include relevant information on HCFC-123 from the *Australian Refrigeration and Air Conditioning Code of Good Practice* (AFCAM, 1997), the MSDS and Australian/New Zealand Standard AS/NZS 1677 – *Refrigeration Systems* (Standards Australia, 1998), and should be reinforced at regular intervals. In particular, training should provide information on acute and chronic effects from exposure to HCFC-123 and should address appropriate control and safety measures required to minimise both occupational and environmental exposure.

For extinguishant maintenance workers, training provided at induction should include relevant information from appropriate Australian Standards (including AS 1851.12 (Standards Australia, 1995a)) and the FPIAA *Code of Practice* (FPIAA, 1995).

For personnel working in areas protected by portable HCFC-blend extinguishants, employers should ensure that adequate training is provided on the safe use of these extinguishants, which should include adequate information on acute health hazards (including first aid) and appropriate warning and instruction on extinguishant discharges in confined work areas.

18.3 Occupational control measures

Under the NOHSC *National Model Regulations and Code of Practice to Control Workplace Hazardous Substances* (NOHSC, 1994c), control measures must be implemented to minimise health risks during handling and use of hazardous substances. With respect to HCFC-123, control measures should be implemented to minimise incidental and accidental exposure to refrigerant and extinguishant vapours.

With regard to the use of HCFC-123 as a *refrigerant* it is recommended that:

- particular attention should be given to engineering control measures and safe work practices aimed at reducing HCFC-123 loss during refrigerant transfer and leak test operations;

- refrigerant and inert gas (usually N_2) mixtures (used in pressure test and leak test operations) should be recovered;
- leak testing should be conducted at least quarterly;
- re-seatable bursting/rupture discs (piped to low pressure side of system) should be installed;
- the use of high efficiency purge equipment and purge filter reprocessing (to recover or recycle HCFC-123) should be encouraged;
- retrofitting existing chiller systems to use HCFC-123 should only be carried out after consultation with equipment and component manufacturers;
- low-level mechanical ventilation should be installed in machine rooms where chillers are operating on HCFC-123 refrigerant;
- where a maintenance technician is required to work at an installation on his/her own, a personal 'motion detector' alarm should be worn.

With regard to the use of HCFC-123 as an *extinguishant* it is recommended that:

- both fixed systems and portable extinguishers containing HCFC-123 should be regularly (at least annually) inspected and tested for proper operation and the inspection report (with recommendations) should be filed with the owner of the equipment;
- extinguishant release mechanisms should be locked (by key) during maintenance and testing of total flooding (fixed) systems;
- employers using portable extinguishers containing HCFC-123 should be required to provide employees with adequate training in their use;
- the sales literature, instructions for use and label of portable fire extinguishers containing HCFC-123 should instruct the operator to evacuate any area into which the extinguishant has been discharged and to delay re-entry until the area has been thoroughly ventilated; and
- the cardiac sensitisation study of the extinguishant blend NAF S-III (Banks, 1997) should not be used as guidance for a health-based design concentration for fixed fire control systems employing NAF S-III as flooding agent as it failed to determine a NOAEL.

18.4 New uses

Under the *Industrial Chemicals (Notification and Assessment) Act 1989* secondary notification is required for any other proposed uses for HCFC-123 other than those assessed in this report (see Section 19).

It is recommended that HCHC-123 not be used as a solvent degreaser or in other industrial applications which may lead to excessive workplace exposure to the chemical. Likewise, HCFC-123 should not be used as a refrigerant in systems where there is a risk of leakage into confined, occupied spaces, such as in vehicle air-conditioning systems.

18.5 Recommendations to NOHSC

18.5.1 Classification

The classification for HCFC-123 recommended in Section 18.1 should be considered by NOHSC for adoption and inclusion in the NOHSC *List of Designated Hazardous Substances* according to the usual process.

18.5.2 Exposure standard

In light of the new human toxicity data reviewed in Section 11.3 it is recommended that NOHSC give priority to the development of a national exposure standard for HCFC-123.

From the information made available for assessment it is recommended that the following data be considered in the further development of this standard:

- the NOAEL for liver effects, determined at 100 ppm (0.6 g/m^3) HCFC-123 in a well-conducted 2-generation reproduction study and supported by other mechanistic and toxicity studies;
- the LOAEL for retarded pup growth in rats, determined at 30 ppm (0.2 g/m^3) HCFC-123 for dams exposed to HCFC-123 throughout a well-conducted 2-generation reproductive toxicity study and independently shown to be a reproducible lactional effect; and
- the occurrence of liver effects in humans following repeated exposure to HCFC-123 at levels (airborne) ranging from 5-500 ppm (0.03-3.0 g/m^3).

It should also be noted that HCFC-123 meets the requirements of the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1998) for classification as a Category 3(b) carcinogen.

There is no indication that a STEL or 'skin notation' should apply.

18.5.3 Health surveillance

Reversible liver effects have been reported in humans following repeated exposure to HCFC-123 at levels ranging from 5-500 ppm. In some cases the effects were limited to elevated AST and ALT levels and were not associated with manifest clinical illness. Further research is needed to establish whether similar effects can be demonstrated in chiller technicians who are routinely exposed to levels of HCFC-123 in the 1-5 ppm range. In the affirmative, atmospheric monitoring might not be sufficient to evaluate exposure to HCFC-123 to chiller technicians and routine health surveillance could be indicated.

Under regulations introduced in Commonwealth, State and Territory government jurisdictions, in accordance with the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), employers are required to provide health surveillance in workplaces where assessment shows that exposure to a hazardous substance may result in an identifiable substance-related disease or adverse health effect.

18.6 Revision of codes of practices and Australian Standards

In order to improve the usefulness of the Australian Refrigeration and Air Conditioning Code of Good Practice (AFCAM, 1997) and the Australian Code of Practice for Design, Installation, Inspection and Testing of Gaseous Fire Extinguishants (FPIAA, 1995), these documents should be revised to provide more information on occupational health and safety, such as health hazards; precautions for use, for example, specifications for personal protective equipment and safe handling information, for example, requirements for storage and disposal of refrigerant and extinguishant products.

The Australian Standard AS 1677 – *Refrigerating Systems* (1986) referred to in PEC4 has been superseded by Australian/New Zealand Standard AS/NZS 1677 (Standards Australia, 1998). The updated standard incorporates relevant features from standards produced by ASHRAE and ISO. Because of the non-flammability and low acute toxicity (LC_{50} by inhalation > 10,000 ppm) of HCFC-123, it is classified as a safety group A1 refrigerant. It is recommended that future revision of Australian/New Zealand Standard AS/NZS 1677 give consideration to the human health effects and animal toxicity of repeated exposure to HCFC-123.

Given the increase in imports of NAF P-III (60% HCFC-123), it is further recommended that future revisions of the Australian/New Zealand Standard for portable extinguishers (AS/NZS 1841.1 (Standards Australia, 1997b)) take into account the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994a).

18.7 Transport

It is recommended that the Federal Office of Road Safety's Advisory Committee for the Transport of Dangerous Goods (ACTDG) consider HCFC-123 for classification as a Class 9 Dangerous Good in view of the following hazardous properties:

- ozone-depleting potential;
- potential acute and chronic health effects; and
- toxic pyrolysis products.

18.8 Environmental protection

Use of HCFC-123 to replace CFCs in cooling applications is recommended on environmental grounds, since the ozone-depleting and global warming potential of the replacement substance is 50 times lower than those for CFCs.

Similarly, the use of extinguishant blends containing HCFC-123 to replace halons in certain firefighting applications is recommended because of the lower or zero ozone depletion potential.

Users should be aware that HCFC-123 is not environmentally innocuous, and that its use will only be acceptable as an interim measure pending development of alternatives with lower ozone depletion potential. Australia's ratification of the Copenhagen amendment to the Montreal Protocol requires that domestic consumption of HCFCs be frozen in 1996, followed by reductions in use of 35%

by 2004, 65% by 2010, 90% by 2015, 99.5% by 2020 and total phase-out by 2030.

In view of the phase-out schedule required by the Copenhagen Amendment to the Montreal Protocol, manufacturers of equipment requiring HCFCs, including HCFC-123, should investigate options for converting to other forms of refrigeration and fire protection technology.

Manufacturers, distributors and users must minimise atmospheric emissions of HCFC-123 by adhering to the *Australian Refrigeration and Air Conditioning Code of Good Practice* (AFCAM, 1997), and the FPIAA's Code of Practice (FPIAA, 1995).

Existing legislative controls on halons and CFCs, including requirements for their recovery and safe disposal, have been extended to HCFCs in most Australian States and Territories.

18.9 Further studies

18.9.1 Toxicological studies

Further research should concentrate on establishing the relevance of the compound-related benign tumours to humans, particularly cholangiofibromas, pancreatic acinar cell adenomas and Leydig (interstitial) cell adenomas. Ideally, a lifetime study should be conducted in a second animal species which the available mechanistic data would indicate to be a more suitable model than the rat for characterising potential carcinogenic effects of HCFC-123 in humans. However, such a study may not be a viable option for a number of reasons, for example, HCFC-123 is only being used as an interim replacement for CFCs.

WY-14643, a known peroxisome proliferator which induces hepatocellular, pancreatic acinar cell and Leydig cell adenomas in rats and does not induce peroxisomes in the pancreas (or Leydig cells), has been shown to cause a mild but sustained increase in serum CCK levels. CCK has been shown to stimulate pancreatic growth and acinar cell carcinogenesis in animals and has also been implicated in the aetiology of human pancreatic cancer. Although CCK levels have been measured in some HCFC-123 studies in animals, the results were inconclusive and it seems warranted to test the hypothesis that HCFC-123 has an effect on CCK in a similar manner to that of WY-14643.

In male and female rats, HCFC-123 has been shown to modulate the function of the hypothalamic-pituitary-gonadal axis in ways that may explain the occurrence of Leydig cell adenomas in male animals. An understanding of the effects of HCFC-123 on sex hormone levels and the hypothalamic-pituitary-gonadal axis in primates would assist in drawing firmer conclusions about the relevance of this tumour for humans.

18.9.2 Monitoring studies

It is recommended that a biological monitoring study be carried out to establish the potential risk of sub-clinical liver effects (elevated levels of circulating liver enzymes without manifest clinical illness) in chiller maintenance technicians who

are subject to repeated exposure to low levels of HCFC-123 (see also the recommendation in Section 18.5.3).

Furthermore, it is recommended that monitoring studies be carried out to establish potential airborne levels of total HCFCs from discharge of HCFC blends from portable (hand-held) extinguishers (3-5 kg), particularly in confined areas.

Quantitative information on yields of thermal degradation products of HCFC-123 and HCFC-blend extinguishants under high temperature conditions would assist in characterising the acute health risk or hazard during exposure.

19. Secondary Notification

design elementUnder the *Industrial Chemicals (Notification and Assessment) Act 1989*, renewed secondary notification of HCFC-123 may be required where an introducer of HCFC-123 becomes aware of any circumstances that may warrant a reassessment of its hazards and risks. Specific circumstances include:

- The function or use of HCFC-123 has increased, or is likely to change, significantly. In particular, notification is required should HCFC-123 or products containing HCFC-123 be used in open industrial processes or in vehicle air-conditioning systems.
- The amount of HCFC-123 introduced into Australia has increased, or is likely to increase, significantly.
- Manufacture of HCFC-123 has begun in Australia.
- Additional information has become available to the introducer as to the adverse health and/or environmental effects of HCFC-123.

The Director (Chemicals Notification and Assessment) must be notified within 28 days of the introducer becoming aware of any of the above circumstances.

APPENDIX 1

Sample Material Safety Data Sheet for HCFC-123

Date of issue	16 March 2001	Page 1	of Total 7

HCFC-123 is classified as Hazardous according to the National Occupational health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1998)].

Company details

Company name	
Address	
State	Postcode
Telephone number	Emergency telephone number
Facsimile number	Telex number

Identification

Product name	2,2-dichloro-1,1,1-trifluoroethane
Other names	HCFC-123
Manufacturer's product code	
UN number	Not allocated
Dangerous goods class and subsidiary risk	Not allocated
Hazchem code	Not allocated
Poisons Schedule number	None allocated
Use	Refrigerant

Physical description and properties

Appearance
Colourless liquid (at 25°C)

Boiling point
27.6°C (at 760 mm Hg)

Freezing point
-107°C

Vapour pressure
89.3 kPa (at 25°C)

Specific gravity
1.46 (at 25°C)

Flashpoint
Does not ignite

Flammability limits
Non-flammable

Solubility in water
2.1 g/L (at 25°C)

Other properties

Odour: Slight ethereal odour.

pH: Neutral

Evaporation Rate: < 1 (CCl_4 = 1.0)

Partition Co-efficient: Log $P_{o/w}$ = 2.3 - 2.9

Ingredients/impurities

Chemical entity	CAS Number	Proportion
HCFC-123	306-83-2	
Impurities		

Health hazard information

HEALTH EFFECTS

Acute

Inhalation: At high concentrations may cause central nervous system and cardiac (sensitisation) effects and liver damage.

Skin: Not irritating to skin in animal studies.

Eye: Slight irritation to eyes in animal studies.

Swallowed: Low acute oral toxicity in animal studies.

Other: At very high concentrations may cause asphyxiation.

Chronic

Inhalation: In humans, repeated exposure to low concentrations has resulted in reversible liver damage and elevated liver enzyme levels. Repeated or prolonged exposure caused liver damage and an increase of benign tumours in animal studies. In animals, repeated exposure reduced the growth of offspring as a result of ingestion of HCFC-123 metabolites in the maternal milk.

Contraindications

Individuals with pre-existing cardiovascular system disease may be predisposed to adverse health effects caused by acute exposure.

Workers who are taking sympathomimetic medication should be warned about potential cardiovascular effects from excessive exposure to HCFC-123.

Regular alcohol consumption may aggravate the adverse health effects from repeated exposure to HCFC-123.

FIRST AID

(Show this MSDS to medical doctor if consulted)

Swallowed: If swallowed no specific intervention is indicated. DO NOT INDUCE VOMITING. Drinking water may be beneficial. Consult a physician if necessary.

Eye: In case of contact with eyes, rinse with plenty of water.

Skin: In case of skin contact wash area with water.

Inhaled: If exposed to high concentrations remove to fresh air. Keep patient calm. If breathing is difficult give oxygen. Give artificial respiration if patient not breathing.

First Aid Facilities

ADVICE TO DOCTOR

No specific antidote. Treat symptomatically.
Use of adrenaline or other catecholamines may be contraindicated. Ventricular arrhythmias may be better treated with beta-blocking agents.

Precautions for use

EXPOSURE STANDARDS

National (Worksafe): In preparation by the National Occupational Health and safety Commission.

International (American Industrial Hygiene Association): 50 ppm (8-hour average).

Industry: Currently 10 ppm (Allied Signal; Elf Atochem).

ENGINEERING CONTROLS

Enclosure of process materials and isolation of reaction vessels with proper design of filling heads should be implemented to limit exposure during manufacture and packaging.

Appropriate fittings should be used for opening/decanting containers.

When opening/decanting/transferring HCFC-123 indoors, local exhaust ventilation should be used.

Approved low-pressure refrigerant recovery/recycle equipment should be used.

Chiller pressure relief devices (refer to AS 1210 and AS/NZS 1677) should be installed and vented to location outside equipment room.

Automated HCFC-123 detector (interlocked with alarm) should be installed at chiller installation site.

PERSONAL PROTECTION

Under normal maintenance conditions no respiratory protection is required.

Respiratory protection (including SCBA) to be *readily available* at chiller installations, storage and filling areas (refer to AS 1319, AS/NZS 1715 and AS/NZS 1716).

Other personal protective equipment to be selected in accordance with appropriate Australian Standards:

Clothing overalls - refer to AS 3765.1 and AS 3765.2.

Gloves - refer to AS/ANZ 2161.

Safety glasses - refer to AS 1336 and AS 1337.

Where a technician is required to work at an installation unassisted, PPE should include a personal 'motion detector/alarm'.

FLAMMABILITY

HCFC-123 is not flammable under conditions of use. Materials with similar chemical structure have been shown to be combustible at low pressure when mixed with air (>60% by volume).

to limit exposure during manufacture and packaging.

Appropriate fittings should be used for opening/decanting containers.

When opening/decanting/transferring HCFC-123 indoors, local exhaust ventilation should be used.

Approved low-pressure refrigerant recovery/recycle equipment should be used.

Chiller pressure relief devices (refer to AS 1210 and AS/NZS 1677) should be installed and vented to location outside equipment room.

Automated HCFC-123 detector (interlocked with alarm) should be installed at chiller installation site.

PERSONAL PROTECTION

Under normal maintenance conditions no respiratory protection is required.

Respiratory protection (including SCBA) to be *readily available* at chiller installations, storage and filling areas (refer to AS 1319, AS/NZS 1715 and AS/NZS 1716).

Other personal protective equipment to be selected in accordance with appropriate Australian Standards:

Clothing overalls – refer to AS 3765.1 and AS 3765.2.

Gloves – refer to AS/ANZ 2161.

Safety glasses – refer to AS 1336 and AS 1337.

Where a technician is required to work at an installation unassisted, PPE should include a personal 'motion detector/alarm'.

FLAMMABILITY

HCFC-123 is not flammable under conditions of use. Materials with similar chemical structure have been shown to be combustible at low pressure when mixed with air (>60% by volume).

Safe handling information

STORAGE and TRANSPORT

Quantities of HCFC-123 stored at chiller installation to be limited to reasonable requirements.

Containers should be stored away from direct sunlight and kept below specified temperature (TO BE SPECIFIED).

Containers should be kept away from incompatible materials (TO BE SPECIFIED).

Empty containers to be stored outside chiller installation or in a well-ventilated location inside.

SPILLS and DISPOSAL

Evacuate area of spill and ventilate by natural or mechanical means, taking care to ventilate low level confined areas.

Contain spill with sand, earth, sawdust or other absorbent material and transfer to steel drum(s) for recovery/disposal.

Product and container to be recovered/held for recycling/ reprocessing or disposal in an approved manner (TO BE SPECIFIED).

FIRE/EXPLOSION HAZARD

Negligible fire hazard when exposed to heat or flame. May decompose in a fire producing toxic vapours of chlorine, hydrogen chloride, hydrogen fluoride, dichloroethylene and phosgene. DO NOT BREATHE FUMES.

Heated containers may generate explosive pressures. Heated containers should be removed (provided they can be removed safely) from hazard area and cooled with water.

No 'Hazchem Code' allocated.

Potentially dangerous interaction may occur with certain materials (TO BE SPECIFIED).

Other information

USE/IMPORTATION INFORMATION

In Australia, the importation and use of HCFC-123 is restricted according to the *Ozone protection Act (1989)*, which is implemented by Environment Australia (EA).

ANIMAL TOXICITY DATA

Acute *oral* (ALD) = 9000 mg/kg bodyweight (rat)

Acute *dermal* (LD_{50}) > 2000 mg/kg bodyweight (rat and rabbit)

Acute *inhalation* ($LC_{50[4h]}$) > 32,000 ppm (rat)

Acute *inhalation* (liver damage – LOAEL) = 1000 ppm (guinea-pig)

Acute *inhalation* (cardiac sensitisation – NOAEL) = 10,300 ppm (dog)

Acute *inhalation* (anaesthetic effects – NOAEL) = 2500 ppm (rat)

HCFC-123 does NOT appear to be genotoxic

Chronic *inhalation* (reduced growth of breast-fed offspring – LOAEL) = 30 ppm (rat)

Chronic *inhalation* (liver effects – NOAEL) = 100 ppm (rat)

Chronic *inhalation* (tumourigenicity – LOAEL) = 300 ppm (rat)

ENVIRONMENTAL DATA

Mobility

HCFC-123 is moderately mobile in soils (soil organic adsorption coefficient = 430) and may contaminate ground water. Spills should be cleaned up immediately.

Persistence

HCFC-123 is not readily biodegradable. It will evaporate quickly from surface water (half-life about 4 hr) but may persist in ground water.

Bioconcentration

HCFC-123 has a low potential for bioaccumulation (estimated bioconcentration factor 10-33).

Aquatic toxicity

HCFC-123 is slightly toxic to aquatic organisms:

Acute (96h) LC_{50} > 350 mg/L (Fathead minnow)

Acute (96h) LC_{50} = 55 mg/L (Rainbow trout)

Acute (48h) immobilisation EC_{50} = 17.3-45.8 mg/L (Daphnia magna)

96-h growth inhibition EC_{50} = 67.8 mg/L (Selenastrum capricornutum)

Ozone depletion

HCFC-123 has an ozone-depleting potential (ODP) of 0.02. It is an interim replacement for CFCs, being scheduled for phase out by 2030 under the Copenhagen Amendment to the Montreal Protocol on Substances that Deplete the Ozone Layer.

Other information

FURTHER INFORMATION

Association of Fluorocarbon Consumers and Manufacturers, The Australian Refrigeration and Air Conditioning Code of Good Practice, Australian Standards, Strathfield, NSW, 1997.
Standards Australia, Australian/New Zealand Standard AS/NZS 1677 - Refrigerating Systems, Homebush, NSW, 1998.
National Industrial Chemicals Notification & Assessment Scheme, 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123), Priority Existing Chemical No. 4: Secondary Notification Assessment, Full Public Report, NOHSC, Sydney, NSW, 1999.

APPENDIX 2

Control Measures for Managing Risks of Exposure to HCFC-123 Refrigerant

A2.1 Engineering controls and equipment design

- Containers (drums) to withstand specified temperature and pressure.
- Appropriate fittings (valve) to refrigerant container during opening.
- Use of approved low-pressure refrigerant recovery/recycle equipment (AS 4211.3).[1,2]
- Appropriate fittings/connections (for example, hoses and vent lines) for refrigerant container during transfer procedures.
- All chiller materials (hoses, gaskets, motor insulation, etc.) to be compatible[3] with HCFC-123.
- Where refrigerant cylinders are manifolded together, single direction flow valves to be used to prevent gravity overfill of cylinders (AS 2030.1).
- Installation of mechanical ventilation[4] at chiller site and refrigerant storage site.
- Appropriate location and air flow for mechanical ventilation system (AS/NZS 1677).
- Use of high efficiency purge unit[5] (in accordance with AFCAM Code of Practice HB-40.1, 1997) for all new and retrofitted chillers.
- Installation of purge monitor (to indicate purging time) (AFCAM, 1997).
- Installation of automated gas bubble (non-condensables) sensor (with alarm) in liquid line of chiller.
- Installation of automated refrigerant sensor/detector (with alarm) at chiller site (AS/NZS 1677) (with period testing).
- Location of sensor/detector(s) in area(s) where refrigerant vapour leaks are most likely, accounting for airflow patterns in equipment room.
- Use of suitably constructed chiller pressure vessels (AS 1210).
- Where pressurisation is used to prevent ingress of air during shutdown of low-pressure chillers, a high pressure limit switch should be installed.
- Installation of pressure relief devices (AS 1210 and AS/NZS 1677) vented to location outside equipment room.

---

[1] The Australian Code (AFCAM, 1997) requires that both refrigerant liquid and vapour be recovered, with pressure reduced to 3 kPa.
[2] To avoid mixing of refrigerants it may be necessary to use dedicated equipment.
[3] HCFC-123 attacks the elastomers present in seals and gaskets used in chillers operating on other refrigerants including C-11.
[4] Interlocked with automated refrigerant detector (AS/NZS 1677).
[5] No Australian Standard developed – ARI Standard 580 (1995) currently used in air-conditioning industry.

- Isolation/stop valves fitted at appropriate locations on compressor, condensor and evaporator (AS 1210).
- Stop valves connecting refrigerant-containing parts to atmosphere to be capped on locked closed when not in use.

A2.2 Safe work practices

- Initial opening of sealed refrigerant containers to be carried out outdoors if possible.
- Proper resealing of refrigerant containers.
- Storage of refrigerant containers below specified temperature.
- Storage of refrigerant containers away from incompatible materials.
- Storage of empty refrigerant containers outside of chiller room (if feasible) away from building ventilation intakes.
- Quantities of refrigerant stored at chiller installation (indoors) to be limited to reasonable requirements (20% of refrigerant charge is recommended) (AS/NZS 1677).
- Quantity of refrigerant (in chiller) required for duty to be kept to a minimum (for example, as computed or as determined by sight glass).
- Prompt clean up of leaks and spills – procedure to be pre-planned.
- Occupancy of chiller installation restricted to personnel with authorised access.
- Entry to plant room carried out under supervision following alarm actuation.
- Care should be taken when working (for extended periods) underneath the chiller as higher concentrations of HCFC-123 vapour are likely to occur at floor level.
- Recovered refrigerant charge to be metered (weight or volume) to ensure maximum recovery.
- Recovery cylinders to be used only as designated (by colour coding, labelling, etc.) and dedicated to HCFC-123 (AS 2030.1).
- Retrofitting a system for HCFC-123 to be carried out after consultation with equipment/component manufacturers (AFCAM Code of Practice HB-40.1, 1997).
- Regular monitoring of chiller integrity by purge system monitoring and regular leak testing.[6]
- Leak testing of connecting pipework to be carried out before charging of refrigerant systems.
- Correct procedures for refrigerant leak testing (AS/NZS 1677).
- Refrigerant and inert gas (usually N_2) mixtures (used in pressure test and leak test operations) to be recovered or as a minimum not to be exhausted into plant room.

[6] At least every three months according to AFCAM Code of Practice (AFCAM, 1997).

- The labelling, colour coding and nameplates for a retrofitted system to be changed to identify new refrigerant and/or lubricant (AS 1319).
- Containers to be properly labelled (NOHSC, 1994a).
- Correct procedures (in compliance with Commonwealth and/or State regulations) for the disposal, transportation and storage of HCFC-123 contaminated oil, oil filters and filter drier cores.
- Refrigerant to be held for reprocessing or disposal in an approved manner (in accordance with appropriate government legislation).
- MSDS to be available at storage facility and chiller installation (NOHSC, 1994b).

A2.3 Personal protective equipment

- Appropriate gloves (AS/NZS 2161), safety glasses (AS/NZS 1336 and AS/NZS 1337) and safety shoes (AS/NZS 2210.2) to be used when handling refrigerant containers.
- Respiratory protection (including self-contained breathing apparatus) to be available at storage facility and outside chiller room (AS 1319, AS/NZS 1715 and AS/NZS 1716).
- A personal 'motion detector' alarm has also been proposed as a requisite part of personal protective equipment. Such an alarm will sound if a worker is immobilised for a pre-set period of time.

A2.4 Note

It should be emphasised that the above is not a listing of each and every control measure relevant to the handling and use of HCFC-123 refrigerants, but comprises the most significant initiatives from information provided for assessment. Relevant Australian codes and standards are quoted in parentheses.

APPENDIX 3

Control Measures for Managing Risks of Exposure to Extinguishants Containing HCFC-123[1]

A3.1 Engineering controls and equipment design

- Extinguishant cylinders to withstand specified pressure (AS 1210 and AS 2030.1).
- Containers to have a reliable means of indicating pressure of contents.
- Appropriate fittings/connections for extinguishant transfer/filling operations (AS 2030.1).
- Specification for both portable extinguishers and fixed systems to meet the Building Code of Australia and a 'compliance certificate' to be obtained from appropriate local government authority.
- Correct specification (AS/NZS 4214.5) for fixed extinguishant 'distribution system' (for example, piping, valves[2], spans and joints and pressure relief devices).
- Compatible system components (for example, piping, valves, pressure relief switches and gauges) for retrofitted extinguishing systems.
- All components to comply with appropriate Australian standards and to be listed by the Commonwealth Scientific Services Laboratory (FPIAA, 1995).
- Appropriate design, installation and commissioning of detection systems (AS 1603.4; AS 1670).
- Extinguishant discharge (for total flooding (fixed) systems) to be completed in specified time (AS/NZS 4214.5).
- Installation of automated mechanical ventilation system (with fixed extinguishant systems) for prompt ventilation after discharge.
- Concentration of discharged extinguishant (for total flooding (fixed) systems) not to exceed specified limits (AS/NZS 4214.5).
- Extinguishant discharge to comply with distribution and holding requirements (AS/NZS 4214.5).
- Quantity of extinguishant in system (that is, primary agent supply) to be the least amount required for the largest single fire hazard protected (FPIAA, 1995).
- Provision for isolation or shutdown of air handling system for 'protected enclosure' (FPIAA, 1995).
- Precautions (for example, sealed openings or automated closures) should be taken to prevent loss of discharged extinguishants to adjacent work areas.

---

[1] NAF S-III (HCFC Blend A) and NAF P-III (HCFC Blend C) are currently the only such extinguishants used in Australia.

[2] Some HCFC extinguishants may not be compatible with the elastomers used in halon system valves.

- Factors resulting in unwanted discharge during testing/service to be thoroughly evaluated and corrected.[3]
- Adherence to 'protected enclosure requirements' (AS/NZS 4214.5).

A3.2 Safe work practices

- Cylinders to be inspected in accordance with government requirements and standards.
- Correct procedure[4] to be followed for filling of extinguishant cylinders (AS 2030.1).
- Extinguishant cylinders to be charged to correct filling ratio/density (AS/NZS 4214.1 and AS/NZS 1841.1).
- Storage of extinguishant containers below specified temperature.
- Storage of extinguishant containers away from incompatible substances.
- Prompt clean up of leaks and spills – procedure to be pre-planned.
- Disposal of extinguishant to be carried out in accordance with appropriate government legislation.
- Maintenance of fire protection equipment according to appropriate standards (AS/NZS 1851.12).
- Extinguishant discharge test carried out according to specified protocol (AS/NZS 4214.1; AS/NZS 1841.1; AS/NZS 1851.12; FPIAA, 1995).
- Commissioning tests for installed systems to be carried out in the presence of occupational safety officer(s) (AS/NZS 4214.1).
- Certification of testing to be provided by installation contractor (AS/NZS 4214.5).
- Retrofitting of existing fire extinguishant equipment with HCFC-123-containing agents should be approved by the appropriate authority.
- Cylinders to be properly marked/labelled (NOHSC, 1994a; AS/NZS 1841.7; AS/NZS 4214.1; FPIAA, 1995).
- MSDS to be available at storage facility (NOHSC, 1994b).

A3.3 Personal protective equipment

- Appropriate gloves (AS/NZS 2161), safety glasses (AS/NZS 1336 and AS/NZS 1337) and safety shoes (AS/NZS 2210.2) to be used when handling and/or filling extinguishant containers.
- Respiratory protection (including self-contained breathing apparatus) to be available at storage facility (AS 1319, AS/NZS 1715 and AS/NZS 1716).
- Appropriate equipment for firefighters (AS/NZS 1715, AS 2375 and AS 4067).

[3] Equipment lockout or service disconnects can be instrumental in preventing false discharges during testing/service.
[4] In accordance with the manufacturer's recommendations.

A3.4 Note

It should be emphasised that the above is not a listing of each and every control measure relevant to the handling and use of HCFC-blend extinguishants, but comprises the most significant initiatives from information provided for assessment. Relevant Australian codes and standards are quoted in parentheses.

APPENDIX 4

Chemical Names, Abbreviations and Synonyms

CDE	2-chloro-1,1-difluoroethene
CFC	chlorofluorocarbon
CFC-11	trichlorofluoromethane
CFC-12	dichlorodifluoromethane
CFC-113	1,1,2-trichloro-1,2,2-trifluoroethane
Cl_2	chlorine
F_2	fluorine
Halon 1211	bromochlorodifluoromethane
Halon 1301	bromodifluoromethane
Halothane	see HCFC-123b1
Halotron	HCFC-123 (>90% plus proprietary additives)
HCFC	hydrochlorofluorocarbon
HCFC-22	chlorodifluoromethane HCFC-
123	2,2-dichloro-1,1,1-trifluoroethane
HCFC-123a	1,2-dichloro-1,1,2-trifluoroethane
HCFC-123b1	1,1,1-trifluoro-2-bromo-2-chloroethane
HCFC-124	1-chloro-1,2,2,2-tetrafluoroethane
HCFC-133a	1-chloro-2,2,2-trifluoroethane
HCFC-141a	1,1-dichloro-1-fluoroethane
HCFC Blend A	see NAF S-III
HCFC Blend C	see NAF P-III
HCl	hydrochloric acid
HF	hydrofluoric acid
HFC	hydrofluorocarbon
HFC-134a	1,1,1,2-tetrafluoroethane
NAF P-III	HCFC-123 (60%); HCFC-124 (28.5%); HFC-134a (7.5%); 4-isopropenyl-1-methylcyclohexene (4%)
NAF S-III	HCFC-22 (82%); HCFC-124 (9.5%); HCFC-123 (4.75%); 4-isopropenyl-1-methylcyclohexene (3.75%)
R-22	see HCFC-22
TFA	trifluoroacetic acid
TFC	trifluoroacetyl chloride
WY-14643	4-chloro-6-(2,3-dimethylphenyl)amino-2-pyrimidinylthio-acetic acid

References

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

AFCAM (1997) The Australian refrigeration and airconditioning code of good practice, part 1: Reduction of emissions of fluorocarbon refrigerants in commercial and industrial refrigeration and airconditioning applications. Strathfield, NSW, Standards Australia.

Allied (1998a) Re: TSCA 8(e) substantial risk information reporting. Letter to the Office of Pollution Prevention and Toxics, US Environmental Protection Agency dated 9 January 1998. Morristown, NJ, AlliedSignal Inc.

Allied (1998b) Subject: HCFC 123. Memorandum dated 7 April 1998. Morristown, NJ, AlliedSignal Inc.

ANZECC (1994) Revised strategy for ozone protection in Australia. ANZECC Report No. 30. Canberra, ACT, Australia and New Zealand Environment and Conservation Council.

ASHRAE (1994) ASHRAE standard 15: Safety code for mechanical refrigeration. Atlanta, Georgia, American Society of Heating, Refrigerating and Air Conditioning Engineers.

Atkinson R, Tuazon EC et al. (1993) Experimental investigations of the products formed from the tropospheric reactions of alternative fluorocarbons, final report. AFEAS Ref. No. D-1199. Riverside, California, Statewide Air Pollution Centre, University of California.

Atkinson RS, Rushman GB et al. (1977) Inhalation of anaesthetic agents. In: Atkinson, RS, Rushman GB et al. A synopsis of anaesthesia. Bristol, J. Wright.

Aviado DM, Micozzi MS (1981) Fluorine-containing organic compounds. In: Clayton GD, Clayton, FE ed. Patty's industrial hygiene and toxicology. New York, Wiley.

Banks C (1997) A study to investigate the potential toxicity of NAF S-III without limonene when administered to beagle dogs via the inhalation route. Report No. 91340 (draft). Senneville, Quebec, Bio-Research Laboratories Ltd.

Barsky FC (1976) *In vitro* microbial mutagenicity studies of 2,2-dichloro-1,1,1-trifluoroethane. Report No. 581-76. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Bentley P, Calder I et al. (1993) Hepatic peroxisome proliferation in rodents and its significance for humans. Food and Chemical Toxicology, 31:857-907.

Biegal LB, Hurtt ME et al. (1992) Comparison of the effects of Wyeth-14,643 in Crl:CD BR and Fischer-344 rats. Fundamental and Applied Toxiology, 19:590-597.

Brashear WT, Ketcha MM et al. (1992) Metabolic identification of halon replacement compounds. Dayton, Ohio, Man Tech Environmental Technology Inc.

Brewer WE, Smith S (1977a) 90-Day subacute inhalation toxicity study with Genetron 123 in Albino rats. Report No. IBT 8562-09344. Morristown, New Jersey, Allied Chemical Corporation.

Brewer WE, Smith S (1977b) Teratogenic study via inhalation with Genetron 123 in albino rats. Report No. IBT 8562-09344. Morristown, New Jersey, Allied Chemical Corporation.

Britelli MR (1975) Eye irritation test in rabbits. Report No. 747-75. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Brock WJ (1988a) Acute dermal toxicity study of HCFC-123 in rabbits. Report No. 578-88. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Brock WJ (1988b) Acute dermal toxicity study of HCFC-123 in rats. Report No. 577-88. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Brock WJ (1988c) Primary dermal irritation study with HCFC-123 in rabbits. Report No. 535-88. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Brusick D (1976) Mutagenicity evaluation of Genetron 123, final report. Project No. 2547. Kensington, Maryland, Litton Bionetics Inc.

Budroe JD, Umemura T et al. (1992) Dose response relationships of hepatic acyl-CoA oxidase and catalase activity and liver mitogenesis induced by the peroxisome proliferator ciprofibrate in C57BL/6N and BALB/c mice. Toxicology and Applied Pharmacology, 113:192-198.

Burgess JL, Crutchfield CD (1995) Tucson fire fighter exposure to products of combustion. Applied Occupational and Environmental Hygiene, 10(1):37-42.

Callander RD (1989) HCFC-123 – an evaluation using the Salmonella mutagenicity assay. Report No. CTL/P/2421. Cheshire, UK, Central Toxicology Laboratory, Imperial Chemical Industries Ltd.

Calm JL (1994) Refrigerant safety – the alternative refrigerants are as safe or safer than those they replace but more care is needed with all refrigerants. ASHRAE Journal, July, pp 17-25.

Carrier (1993) Personal communication, Carrier Canada Ltd.

Checket-Hanks B (1991) R-22 leak at ice rink kills one, injures 34. Air-Conditioning, Heating and Refrigeration News, 27 May:1-2.

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 (1964) Preliminary studies on the inhalation toxicity of technical (70.9 per cent) 1,1-dichloro-2,2,2-trifluoroethane. Report No. 151-64. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Clayton JW (1966) Acute inhalation toxicity. Report No. 16-66. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Clegg ED, Cook JC et al. (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, final report. Project No. M165-162. Virginia, Hazleton Laboratories America Inc.

Cohen SD, Pumford NR et al. (1997) Selective protein covalent binding and target organ toxicity. Toxicology and Applied Pharmacology, 143:1-12.

Commonwealth Fire Board (1994) Halon fire extinguishants: Alternative fire protection strategies. Melbourne, VIC, Commonwealth Fire Board.

Cook JC, Mullin LS et al. (1993) Investigation of a mechanism for Leydig cell tumorigenesis by linuron in rats. Toxicology and Applied Pharmacology, 119:195-204.

Coombs DW (1994) HCFC-123 – 13-week inhalation neurotoxicity study in the rat. Report No. ALS3/931038. Cambridgeshire, UK, 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). Report No. 227-76. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

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

Darr RW (1981) An acute inhalation toxicity study of Fluorocarbon 123 in the Chinese hamster. Report No. MA-25-78-15. Morristown, New Jersey, Corporate Medical Affairs, Allied Corporation.

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

Deutsche Forschungsgesellschaft (1994) List of MAK and BAT values. Bonn, Germany, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area.

Dodd DE, Brashear WT et al. (1993) Metabolism and pharmacokinetics 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). Report No. 229-78. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Du Pont (1993) Workplace guidelines for SUVA® Centri-LP (HCFC-123) in refrigeration and air conditioning applications. Wilmington, Delaware, Du Pont Chemicals Customer Service Center.

Du Pont (1998) Personal communication, Du Pont (Australia) Pty Ltd.

ECETOC (1996) Joint assessment of commodity chemicals No. 33: 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123). Brussels, Belgium, European Centre for Ecotoxicology and Toxicology of Chemicals.

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

Elf Atochem (1998) Personal communication, Elf Atochem (Australia) Pty Ltd.

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.

EPA (1995) The phase-out of hydrochlorofluorocarbons in Australia. Canberra, ACT, Environment protection Agency.

Federal Office of Road Safety (1998) Australian code for the transport of dangerous goods by road and rail, 6th ed. Canberra, ACT, Australian Government Printing Service.

Ferrera R, Tolando R et al. (1997) Cytochrome P450 inactivation during reductive metabolism of 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123) by phenobarbital- and pyridine-induced rat liver microsomes. Toxicology and Applied Pharmacology, 143:420-428.

Filicheva AP (1975) Changes in the nervous system following chronic action of fluorinated aliphatic hydrocarbons (Russian). Gigiena Truda i Professional'nye Zabolevaniya, 10:14-16.

Fisher DA, Hales CH et al. (1990a): Model calculations of the relative effects of CFCs and their replacements on stratospheric ozone. Nature, 344:508-512.

Fisher DA, Hales CH et al. (1990b): Model calculations of the relative effects of CFCs and their replacements on global warming. Nature, 344:513-516.

FPIAA (1995) Code of practice for the design, installation and testing of gaseous fire suppression systems utilising ozone depleting substances. Roseberry, NSW, Fire Protection Industry Association of Australia.

Godin CS, Drerup JM et al. (1993) Conditions influencing the rat liver microsomal metabolism of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). Drug Metabolism and Disposition, 21:551-553.

Goodman NC (1975) Primary skin irritation and sensitization tests on guinea pigs. Report No. 149-76. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Grasso P, Hinton RH (1991) Evidence for a possible mechanisms of non-genotoxic carcinogenesis in rodent liver. Mutation Research, 248:271-290.

Hall GT, Moore BL (1975) Acute inhalation toxicity on Freon 123. Report No. 426-75. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Harris JW, Jones JP et al. (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(5):720-725.

Harris JW, Pohl LR et al. (1991) Tissue acylation by the chlorofluorocarbon substitute 2,2-dichloro-1,1,1-trifluoroethane. Proceedings of the National Academy of Science, 88:1407-1410.

Hayman GD, Johnson, CE (1992) Tropospheric modelling studies related to the degradation of replacement compounds. AFEAS Workshop Proceedings: Atmospheric wet and dry deposition of carbonyl and haloacetyl halides. Washington, DC, AFEAS Program Office.

Heinrich U (1996) Crossover study with HFCF 123 in lactating Sprague-Dawley rats including additional studies on milk production and metabolites in offspring urine. Report No. 95/9. Hannover, Germany, Fraunhofer Institute of Toxicology and Aerosol Research

Helas G, Wilson SR (1992) On sources and sinks of phosgene in the troposphere. Atmospheric Environment, 26A:2975-2982.

Henry JE (1975) Acute oral test on FC-123. Report No. 638-75. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Hoet P, Graf MLM et al. (1997) Epidemic of liver disease caused by hydrochlorofluorocarbons used as ozone-sparing substitutes of chlorofluorocarbons. Lancet, 350:556-559.

Hoffman JS (1990) Replacing CFCs: The search for alternatives. Ambio, 19:329-333.

Hofmann T (1995) HCFC 123, HCFC 141B and HCF 134a, testing for subacute (2 weeks) inhalation toxicity in male and female Sprague Dawley rats. Report No. 95.0347. Frankfurt am Main, Germany, Hoechst Aktiengesellschaft.

Hubbard KA, Roth TP et al. (1991) A potential role for immunological mechanisms in halothane hepatotoxicity. In: Meeks RG, Harrison SD et al. ed. Hepatotoxicology. Florida, CRC Press, pp 647-665.

Hughes EW (1994) HCFC 123: A study of the effect on reproductive function of two generations in the rat. Report No. ALS 5/932336. Huntingdon, UK, Huntingdon Research Centre Ltd.

IARC (1987) IARC Monographs on the evaluation of the carcinogenic risks to humans, Supplement 7. Lyon, France, International Agency for Research on Cancer.

IARC (1995) Peroxisome proliferation and its role in carcinogenesis: Views and expert opinions of an IARC Working Group on Peroxisome Proliferation, Lyon, 7-11 December 1994. Lyon, France, International Agency for Research on Cancer.

IPCS (1990) Fully halogenated chlorofluorocarbons (ethane derivatives). IPCS Environmental Health Criteria Report No. 113. Geneva, Switzerland, International Programme on Chemical Safety, World Health Organization.

IPCS (1992) Partially halogenated chlorofluorocarbons (ethane derivatives). IPCS Environmental Health Criteria Report No. 139. Geneva, Switzerland, International Programme on Chemical Safety, World Health Organization.

IPCS (1998) Limonene. Concise International Chemical Assessment Docuemnt No. 5. Geneva, Switzerland, International Programme on Chemical Safety, World Health Organization.

Jamison KC, Larson JL et al. (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 (No. 91/PFE008/0477). Eye, Suffolk, Life Sciences Research Ltd.

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

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

Jenkins CA (1992d) HCFC-123: Determination of its EC50 to *Selenastrum capricornutum* (No. 91/PFE007/0935). Eye, Suffolk, Life Sciences Research Ltd.

Kanakidou M, Dentener FJ et al. (1992) A global three-dimensional study of the distribution of HCFC-22 and its oxidation products in the troposphere. AFEAS Workshop Proceedings: Atmospheric wet and dry deposition of carbonyl and haloacetyl halides. Washington, DC, AFEAS Program Office.

Keller DA (1995) Biochemical studies of peroxisome proliferation and related endpoints in rats exposed by inhalation to HFC-134a, HCFC-141b, and HCFC-123. Report No. 57-95. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Keller DA (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, 21:505-415.

Kelly DP (1975) Two-week inhalation toxicity study with cover sheet and letter. Report No. 149-76. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Kelly DP (1989) Four-week inhalation toxicity study with HCFC-123 in rats. Report No. HLR 229-89. Newark, Delaware, Haskell Laboratory, 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. Report No. CTL/P/3807. Cheshire, UK, Zeneca Ltd.

Klotz U, Ammon E (1998) Clinical and toxicological consequences of the inductive potential of ethanol. European Journal of Clinical Pharmacology, 54:7-12.

Lerman Y, Winkler E. et al. (1991) Fatal accidental inhalation of bromochlorodifluoromethane (Halon 1211). Human and Experimental Toxicology, 10:125-128.

Lesage S, Brown S et al. (1992) Degradation of chlorofluorocarbon-123 under anaerobic conditions. Chemosphere, 24:1225-1243.

Lewis RW (1990) 28-Day inhalation study to assess changes in rat liver and plasma. Report No. CTL/T/2706. Cheshire, UK, Central Toxicology Laboratory, Imperial Chemical Industries Ltd.

Lieder P, Cook J et al. (1993) Similarities in peroxisome proliferation and biochemical effects between HCFC-123 and halothane (HCFC-123b1) in rats. The Toxicologist, 13:396.

Lind RC, Gandolfi AJ et al. (1995) Biotransformation and hepatotoxicity of HCFC-123 in the guinea pig: Potentiation of hepatic injury by prior glutathione depletion. Toxicology and Applied Pharmacology, 134:175-181.

Liu RCM, Hurtt ME et al. (1996) Effect of the peroxisome proliferator, ammonium perfluorooctanoate (C8), on hepatic aromatase in adult male Crl:CD BR (CD) rats. Fundamental and Applied Toxicology, 30:220-228.

Loizou CA, Urban G et al. (1994) Gas-uptake pharmacokinetics of 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123). Drug Metabolism and Disposition, 20(4):511-517.

Longnecker DS, Sumi C (1990) Effects of sex steroid hormones on pancreatic cancer in the rat. International Journal of Pancreatology, 7:159-165.

Longstaff E, Robinson M et al. (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.

Lunam CA, Cousins MJ et al. (1985) Guinea pig model of halothane-associated hepatotoxicity in the absence of enzyme induction and hypoxia. Journal of Pharmacology and Experimental Therapeutics, 232:802-809.

Malley LA (1990) Subchronic inhalation toxicity: 90-Day study with HCFC-123 in rats. Report No. 594-89. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Malley LA (1992) Combined chronic toxicity/oncogenicity study with HCFC-123: Two-year inhalation toxicity study in rats. Report No. 699-91. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Malley LA, Carakostas M et al. (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 et al. (1994) Hepatotoxicity in guinea pigs following acute exposure to 1,1-dichloro-2,2,2-trifluoroethane. Toxicologic Pathology, 22(4):404-414.

Marshal RR (1991) Evaluation of chromosome aberration frequencies in cultured peripheral blood lymphocytes from rats treated with HCFC-123. Study No. ASU 1/RLC. Harrogate, Yorkshire, Hazleton Microtest.

Martin JL (1993) Immunochemical techniques for the detection of tissue target macromolecules of reactive metabolites of halothane and hydrofluorocarbons. ISSX Newsletter, 12(1).

Mellor R, Boglu D et al. (1993) Absorption cross-sections and photolysis studies of halogenated carbonyl compounds, photooxidation studies on CF3 containing CFC substitutes. AFEAS Workshop Proceedings: Kinetics and metabolisms for the reactions of halogenated organic compounds in the troposphere. Washington, DC, AFEAS Program Office.

Messina M, Messina V (1991) Increasing use of soyfoods and their potential role in cancer prevention. Journal of the American Dietetic Association, 91:836-40

Mostofi FK, Price EB (1973) Tumors of the male genital system. Washington, D.C., Armed Forces Institute of Pathology.

MSA (1998) Personal communication, MSA Pty Ltd.

Muller W, Hofmann, T (1988) HCFC-123 – micronucleus test in male and female NMRI mice after inhalation. Study No. 88.0372. Frankfurt am Main Germany, Hoechst Aktiengesellschaft.

Mullin LS (1976) Behavioural toxicity testing of Fluorocarbon 123 in rats. Report No. 941-76. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

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

National Health and Medical Research Council (1997) Standard for the uniform scheduling of drugs and poisons, No. 12. Canberra, ACT, Australian Government Publishing Service.

NFPA (1996) NFPA 2001: Standard on clean agent fire extinguishing systems. Quincy, Massachusetts, National Fire Protection Association.

NICNAS (1996) 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123): Priority Existing Chemical No. 4: Full Public Report. Canberra, ACT, Australian Government Publishing Service.

NICNAS (1999) Handbook for notifiers. Sydney, NSW, National Industrial Chemicals Notification and Assessment Scheme.

NOHSC (1994a) National code of practice for the labelling of workplace hazardous substances. Canberra, ACT, Australian Government Publishing Service.

NOHSC (1994b) National code of practice for the preparation of material safety data sheets. Canberra, ACT, Australian Government Publishing Service.

NOHSC (1994c) National model regulations and code of practice for the control of workplace hazardous substances. Canberra, ACT, Australian Government Publishing Service.

NOHSC (1998) Approved criteria for classifying hazardous substances (draft). Canberra, ACT, Australian Government Publishing Service.

North American Fire Guardian Technology (1998) Personal communication, North American Fire Guardian Technology Pty Ltd.

Obourn JD, Frame SR et al. (1997) Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. Toxicology and Applied Pharmacology, 145:425-436.

OECD (1981) Guidelines for the testing of chemicals. Paris, France, Organization for Economic Cooperation and Development.

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

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

Prinn RG, Golombek A (1990) Global atmospheric chemistry of CFC-123. Nature, 344:47-49.

Procter NH, Hughes JP et al. (1989) Chemical hazards of the workplace. New York, New York, Van Nostrand Reinhold.

Purchase IFH, Ashby J et al. (1994) Mechanistically-based human assessment of peroxisome proliferator-induced hepatocarcinogenesis. Human and Experimental Toxicology, 13, Supplement 2.

Raventos J, Lemon PG (1965) The impurities in fluothane: Their biological properties. British Journal of Anaesthesiology, 37:716-737.

Ray DC, Drummond GB (1991) Halothane hepatitis. British Journal of Anaesthesia, 67:84-99.

Sandow J, Jerabek-Sandow G et al. (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). Report 7/95. Frankfurt am Main, Germany, Hoechst Aktiengesellschaft.

Sandow J, Rechenberg W et al. (1995b) Effect of HCFC-123 on androgen biosynthesis and gonadotropin secretion in rats. Report No. 1/94. Frankfurt am Main, Germany, Hoechst Aktiengesellschaft.

Schroeder R (1989a) An inhalation development toxicity study in rabbits with HCFC-123, final report. Project No. 88-3304. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Schroeder R (1989b) An inhalation range-finding study to evaluate the toxicity of HCFC-123 in the pregnant rabbit, final report. Project No. 88-3303. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Schwarzbach S (1995) CFC alternatives under a cloud. Nature, 376:297-298.

Slauter RW (1997) HCFC 123: Inhalation study in pregnant monkeys to assess milk transfer and composition following postpartum exposure. Report No. 125-042. Mattawan, Michigan, MPI Research.

Standards Australia (1994a) Australian standard AS 1319: Safety signs for the occupational environment. Homebush, NSW, Standards Australia.

Standards Australia (1994b). Australian/New Zealand standard AS/NZS 1715: Selection, use and maintenance of respiratory protective devices. Homebush, NSW, Standards Australia.

Standards Australia (1994c). Australian/New Zealand standard AS/NZS 1716: Respiratory protective devices. Homebush, NSW, Standards Australia.

Standards Australia (1995a) Australian standard AS 1851.12: Maintenance of fire protection equipment – gaseous fire extinguishing systems. Homebush, NSW, Standards Australia.

Standards Australia (1995b) Australian/New Zealand standard AS/NZS 4214.1: General requirements for gaseous fire extinguishing systems. Homebush, NSW, Standards Australia.

Standards Australia (1995c) Australian/New Zealand standard AS/NZS 4214.5: Gaseous fire extinguishing systems - NAF S-III (HCFC Blend A) total flooding systems. Homebush, NSW, Standards Australia.

Standards Australia (1995d) Australian/New Zealand standard AS/NZS 4214.12: Maintenance of fire protection equipment - gaseous fire extinguishing systems. Homebush, NSW, Standards Australia.

Standards Australia (1997a). Australian/New Zealand standard AS/NZS 1841.1: Portable fire extinguishers – general requirements. Homebush, NSW, Standards Australia.

Standards Australia (1997b). Australian/New Zealand standard AS/NZS 1841.7: Portable fire extinguishers – specific requirements for vaporizing-liquid type extinguishers. Homebush, NSW, Standards Australia.

Standards Australia (1997c). Australian/New Zealand standard AS/NZS 1850: Portable fire extinguishers – classification, rating and performance testing. Homebush, NSW, Standards Australia.

Standards Australia (1998) Australian/New Zealand Standard AS/NZS 1677: Refrigerating systems. Homebush, NSW, Standards Australia.

Standley L, Bott T (1998) Trifluoroacetate, an atmospheric breakdown product of hydrofluorocarbon refrigerants: Biomolecular fate in aquatic organisms. Environmental Science and Technology, 32:469-475.

Takebayashi T, Kabe I et al. (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 et al. (1998b) Exposure to 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) and acute liver dysfunction: A causal inference. Journal of Occupational Health, 40:334-338.

Takebayashi T (1999) Personal communication.

Tanaka S, Kabe I et al. (1998) Environmental and biological monitoring of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). Journal of Occupational Health, 40:348-349.

Trochimowicz HJ, Mullin LS (1973) Cardiac sensitization potential (EC_{50}) of trifluoro-dichloroethane. Report No. 132-73. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

Trochimowicz HJ, Moore BL et al. (1977) Subacute inhalation toxicity studies on eight fluorocarbons (abstract). Toxicology and Applied Pharmacology, 41:198-199.

Tromp T, Ko M et al. (1995) Potential accumulation of a CFC replacement degradation product in seasonal wetlands. Nature, 376:327-330.

Tucker MJ, Orton TC (1995) Comparative toxicology of hypolipidaemic fibrates. London, Taylor & Francis.

Urban G, Dekant W (1994) Metabolism of 1,1-dichloro-2,2,2-trifluoroethane in rats. Xenobiotica, 24(9):881-892.

Urban G, Speerschneider P et al. (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(2):170-176.

US EPA (1994a) Clean air act final rule: Protection of stratospheric ozone (59FR 13044). Washington DC, Environmental Protection Agency.

US EPA (1994b) SNAP technical background document: Risk screen on the use of substitutes for class 1 ozone-depleting substances, fire suppression and explosion protection (halon substitutes). Washington DC, Office of Air and Radiation, Stratospheric Protection Division.

Van Dijk NRM (1992) Adsorption of sodium trifluoroacetate (NaTFA) to three different soils. AFEAS Contract No. CTR SP91-18.2. Graveland, The Netherlands, Solvay Duphar.

Van Ginkel CG, Stroo CA (1993) Biodegradability of trifluoroacetic acid, sodium salt in the closed bottle test. AFEAS Ref. No. D-1216. Arnhem, The Netherlands, Akzo Research Laboratories.

Verlinden N (1997) Personal communication.

Vinegar A, Williams RJ et al. (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.

Visscher PT, Culbertson CW et al. (1994) Degradation of trifluoroacetate in oxic and anoxic sediments. Nature, 369:729-731.

Warheit DB (1993) Mechanistic studies with HCFC-123. Report No. 828-92. Newark, Delaware, Haskell Laboratory, Du Pont de Nemours and Co.

WMO (1995) Scientific assessment of ozone depletion, Global ozone research and monitoring project report No. 37. Geneva, Switzerland, World Meteorological Organisation.

WorkCover Authority of New South Wales and Worksafe Australia (1993) A survey of industrial solvent use in the Rockdale area. Canberra, ACT, Australian Government Publishing Service.

Woutersen RA, Van Garderen-Hoetmer A et al. (1991) Early indicators of exocrine pancreas carcinogenesis produced by non-genotoxic agents. Mutation Research, 248:291-303.

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

Zakhari S, Aviado DM (1982) Cardiovascular toxicology of aerosol propellants, refrigerants and related solvents. In: Van Stee, EW ed. Cardiovascular toxicology. New York, Raven Press, pp 281-314.