1,1,1,2-Tetrafluoroethane (HFC-134a)  
(CAS No. 811-97-2)  
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1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)

CONTENTS

EXECUTIVE SUMMARY 1

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS 3

1. SUMMARY AND CONCLUSIONS 4

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS 6

2.1 Identity 6
2.2 EU classification and labelling 6
2.3 Physical and chemical properties 6
2.4 Conversion factors 8
2.5 Analytical methods 8

3. PRODUCTION, STORAGE, TRANSPORT AND USE 9

3.1 Production 9
3.2 Storage 9
3.3 Transport and handling 9
3.4 Use 10

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION 12

4.1 Emissions 11
  4.1.1 Natural sources 11
  4.1.2 Emissions during production and use 11
4.2 Environmental distribution 11
4.3 Environmental fate and biotransformation 12
  4.3.1 Atmospheric fate and impact 12
  4.3.2 Environmental impact of atmospheric degradation products of HFC-134a 16
  4.3.3 Contribution of HFC-134a to environmental trifluoroacetic acid 17
  4.3.4 Aquatic fate 18
  4.3.5 Terrestrial fate 18
  4.3.6 Biodegradation 19
  4.3.7 Bioaccumulation 19

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE 20

5.1 Environmental levels 20
5.2 Human exposure levels and hygiene standards 20
  5.2.1 Non-occupational exposure 20
  5.2.2 Occupational exposure 20
  5.2.3 Hygiene standards 20
6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Bacteria 22
6.2 Invertebrate aquatic species 22
6.3 Fish 22
6.4 Summary and evaluation 22

7. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION

7.1 In vivo 23
7.2 In vitro 24
  7.2.1 Physiologically-based pharmacokinetic modelling 25
7.3 Summary 25

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure 26
  8.1.1 Narcotic potential 27
  8.1.2 Cardiac sensitisation 27
8.2 Skin and eye irritation, sensitisation 28
  8.2.1 Skin irritation 28
  8.2.2 Eye irritation 28
  8.2.3 Skin sensitisation 29
8.3 Repeated exposure 29
8.4 Genotoxicity and cell transformation 29
  8.4.1 In vitro 30
  8.4.2 In vivo 32
  8.4.3 Cell transformation in vitro 34
  8.4.4 Summary 35
8.5 Chronic toxicity and carcinogenicity 35
  8.5.1 Mechanistic studies 36
8.6 Reproductive effects, embryotoxicity and teratology 40
  8.6.1 Fertility 40
  8.6.2 Embryotoxicity and teratology 41
8.7 Neurological studies 42

9. EFFECTS ON HUMANS 44

LIST OF SPECIAL ABBREVIATIONS 45

BIBLIOGRAPHY 47

References quoted 47
References not quoted 58

APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES 60
<table>
<thead>
<tr>
<th>Appendix/Beta</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPENDIX B: NAMING AND NUMBERING SYSTEM FOR FLUOROCARBON COMPOUNDS</td>
<td>61</td>
</tr>
<tr>
<td>APPENDIX C: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR</td>
<td>64</td>
</tr>
<tr>
<td>MEMBERS OF THE TASK FORCE</td>
<td>65</td>
</tr>
<tr>
<td>MEMBERS OF THE SCIENTIFIC COMMITTEE</td>
<td>66</td>
</tr>
</tbody>
</table>
**EXECUTIVE SUMMARY**

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It updates an earlier ECETOC review and presents a critical evaluation of the available data on the ecotoxicity, toxicity, environmental fate and impact of 1,1,1,2-tetrafluoroethane (HFC-134a), including results of recent and unpublished studies conducted by the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT).

1,1,1,2-Tetrafluoroethane (HFC-134a) is a colourless, non-flammable gas that is mainly used, alone or blended with other components, to replace hydrochlorofluorocarbons in refrigeration and air conditioning at home, in cars and in industry. Although HFC-134a has a high global warming potential, its contribution to the greenhouse effect is, currently, insignificant due to its low atmospheric concentration. HFC-134a does not cause ozone depletion because it does not contain chlorine or bromine. Any HFC-134a released to the environment will rapidly volatilise to the atmosphere, where it is slowly degraded to trifluoroacetic acid, formic acid, hydrofluoric acid and carbon dioxide. Trifluoroacetic acid is relatively stable in the environment.

The toxicity of HFC-134a to experimental animals is extremely low. After a single brief exposure to the gas, narcosis may occur at very high concentrations (500,000 ppm; 2,080,000 mg/m³). HFC-134a also causes slight skin or eye irritation, but it is not a skin sensitisier. Exposure to high levels of HFC-134a (80,000 ppm; 334,000 mg/m³) can induce cardiac sensitisation to adrenaline. HFC-134a has no adverse effects on fertility or foetal development and shows no non-neoplastic target organ toxicity in long-term inhalation studies in rats exposed to up to 50,000 ppm (208,000 mg/m³) for 1 year.

HFC-134a is not genotoxic in vitro or in vivo. No tumours due to HFC-134a were seen in rats dosed with HFC-134a by gavage (dissolved in corn oil) for 1 year, or in female rats following daily inhalation for 2 years. In the latter study, male rats inhaling 50,000 ppm showed increases in the incidence of testicular Leydig cell hyperplasia and benign Leydig cell adenoma. These tumours were most likely to have been induced by a non-genotoxic mechanism and are of no significance for humans. Therefore, it is considered that HFC-134a does not present a carcinogenic risk to humans at any foreseeable levels of exposure.

HFC-134a has been used as a propellant in metered dose inhalers for several years. There are no known effects resulting from this type of exposure to HFC-134a in humans.

---

a ECETOC (1995). Joint Assessment of Commodity Chemicals No. 31
b A cooperative research effort (1987-2000) sponsored by 16 of the leading CFC producers [www.afeas.org/paft/]

HFC-134a has a low toxicity to aquatic organisms such as trout and water fleas (*Daphnia*). Although practically non-biodegradable, HFC-134a is unlikely to have any impact on the aquatic environment because of its high volatility and low potential for bioaccumulation.
THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple use) are jointly reviewed by experts from a number of companies with knowledge of the chemicals. Only the chemical itself is considered in a JACC review; products in which it appears as an impurity are not normally taken into account.

This document presents a critical evaluation of the toxicology and ecotoxicology of 1,1,1,2-tetrafluoroethane (HFC-134a; CAS No. 811-97-2).

Where relevant, the Task Force has graded the studies by means of a "code of reliability" (CoR) (Appendix A) to reflect the degree of confidence that can be placed on the reported results.
1. SUMMARY AND CONCLUSIONS

1,1,1,2-Tetrafluoroethane (HFC-134a) is a non-flammable, colourless gas with a faint ethereal odour. It was developed as a substitute for fully halogenated chlorofluorocarbons and for partially halogenated hydrochlorofluorocarbons. Its main current applications are in refrigeration and air conditioning (domestic, automotive and industrial), in which it is used either alone or as a component of blends.

HFC-134a, when released to the environment, will enter almost exclusively into the ambient air; it has little tendency to partition to biota or soil. Because of its moderate sorption affinity, HFC-134a is expected to be mobile in soil. Atmospheric degradation of HFC-134a occurs mainly in the troposphere by reaction with hydroxyl radicals leading to trifluoroacetic acid, formic acid, hydrofluoric acid and carbon dioxide as ultimate degradation products. Trifluoroacetic acid appears to be rather stable in environmental conditions and is known to be naturally occurring. The overall atmospheric lifetime of HFC-134a is estimated to range from 13.6 to 14.0 years. HFC-134a has a global warming potential of 1,300 relative to carbon dioxide (= 1). The actual contribution of HFC-134a to the greenhouse effect is, currently, insignificant (0.14% of that of carbon dioxide) due to its low atmospheric concentration (13.6 ppt).

The acute toxicity of HFC-134a to aquatic organisms is low: the EC50 is 980 mg/l for Daphnia and the LC50 450 mg/l for trout. Although practically no (2 to 3% after 28 days) biodegradation has been observed, the high volatility and low bioaccumulation potential of HFC-134a make any impact on the aquatic environment highly unlikely.

In mammalian species, HFC-134a is rapidly absorbed and equilibrated in tissues after inhalation and is eliminated from the blood in expired air with a half-life of a few minutes. Metabolism to trifluoroacetic acid occurs only in minor amounts.

HFC-134a has an extremely low order of acute toxicity. The lowest concentration resulting in death following a 4-hour exposure has been reported to be 567,000 ppm (2,360,000 mg/m³) in rats. The symptoms of acute intoxication are characterised by central nervous effects due to narcotic properties, seen only at extremely high exposure concentrations (500,000 ppm; 2,080,000 mg/m³).

When HFC-134a is in contact with cutaneous or ocular mucosal membranes, it causes slight irritation, which is possibly a consequence of the test procedures. It is not a skin sensitiser.

HFC-134a can induce cardiac sensitisation in dogs at 80,000 ppm (334,000 mg/m³) after an exogenous adrenaline challenge.

* The naming and numbering system for fluorocarbons is explained in Appendix B
HFC-134a showed no adverse effects on fertility in a dominant lethal study in mice. It was not teratogenic in rats and rabbits, and showed no reproductive effects in a two-generation fertility study in rats. Only non-specific effects on foetal maturation (delayed ossification of the foetus) in the rat were observed following exposure to 50,000 ppm HFC-134a (208,000 mg/m³) and above.

HFC-134a was not genotoxic in vitro or in vivo in a large variety of studies including all important endpoints.

The chronic toxicity of HFC-134a was investigated in rats exposed by inhalation to concentrations of up to 50,000 ppm (208,000 mg/m³) for 2 to 52 weeks. No toxicologically significant effects were seen in these studies. No treatment-related non-neoplastic lesions were seen in rats or in mice exposed (1 h/d) to concentrations of 0, 2,500, 10,000 or 50,000 ppm HFC-134a (0, 10,400, 41,700, 208,000 mg/m³) for 108 weeks or 106 weeks, respectively.

Two carcinogenicity studies were conducted. In a limited study (52 weeks of treatment) in rats with daily oral administration (in corn oil) of 300 mg HFC-134a/kgbw, no tumorigenic effect was seen during the 16-month post-treatment observation period. In another study in rats with daily inhalation exposures of up to 50,000 ppm (208,000 mg/m³) for 104 weeks, HFC-134a did not produce neoplastic changes in female rats. In male rats exposed to 50,000 ppm, slight increases in the incidence of testicular Leydig cell hyperplasia and benign Leydig cell adenomas were observed. As HFC-134a is not genotoxic, these changes are most likely to be due to a non-genotoxic, hormonally-based mechanism, e.g. due to an effect on pituitary function and prolactin secretion, and are of no significance for humans. Therefore, it is considered that HFC-134a does not present a carcinogenic risk to humans at any foreseeable levels of exposure.

There are no reports of adverse effects in humans exposed to HFC-134a.

An occupational exposure limit (8-hour time-weighted average) of 1,000 ppm (4,170 mg/m³) is recommended by a number of occupational exposure standard-setting authorities.
2. IDENTIFY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name: 1,1,1,2-Tetrafluoroethane

IUPAC name: 1,1,1,2-Tetrafluoroethane

Synonyms: Fluorocarbon 134a
HFC-134a
HFA-134a
Norflurane
Tetrafluoroethane

CAS name: Ethane, 1,1,1,2 - tetrafluoro-

CAS registry number: 811-97-2

EC (EINECS) number: 212-377-0

Formula: C₂H₂F₄

Molecular mass: 102.0

Chemical structure:

\[
\begin{array}{c}
F & & F \\
\downarrow & & \downarrow \\
C & - & C \\
\downarrow & & \downarrow \\
H & & F
\end{array}
\]

2.2 EU classification and labelling

HFC-134a is not classifiable according to the Dangerous Substances Directive 67/548/EEC (EC, 1993).

2.3 Physical and chemical properties

HFC-134a is a colourless, non-flammable gas at room temperature and normal atmospheric pressure. It has a faint ethereal odour and is slightly soluble in water. Physical and chemical properties are given in Table 1.
**Table 1: Physical and chemical properties**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value, unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>–108°C</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>Boiling point at 1,013 hPa</td>
<td>–26°C</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>Relative density of liquid, D₂²⁰</td>
<td>1.207</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>(density of water at 4°C is 1,000 kg/m³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscosity of liquid at 20°C</td>
<td>Not applicable</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>Refractive index of liquid n₂ at 20°C</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td>Vapour pressure at 20°C</td>
<td>5,700 hPa</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>at 25°C</td>
<td>6,619 hPa</td>
<td>Du Pont, 2002</td>
</tr>
<tr>
<td>Vapour density at 20°C (air = 1)</td>
<td>3.52</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>Threshold odour concentration</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Surface tension at 20°C</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Solubility in water at 25°C and 1,013 hPa</td>
<td>1.0 g/l</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td></td>
<td>1.5 g/l</td>
<td>Du Pont, 2002</td>
</tr>
<tr>
<td>Miscibility with acetone, ethanol and petroleum solvents</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Partition coefficient, log Kₗₒₚ (octanol/water) at 20°C</td>
<td>1.06⁴</td>
<td>PAFT, 1990</td>
</tr>
<tr>
<td>Partition coefficient, log Kₗₒₚ (organic carbon/water) at 20°C</td>
<td>0.96⁴</td>
<td></td>
</tr>
<tr>
<td>Henry’s Law constant at 25°C</td>
<td>10,220 Pa·m³/mol</td>
<td>Calculated ⁵ (1.0 g/l)</td>
</tr>
<tr>
<td></td>
<td>6,900 Pa·m³/mol</td>
<td>Calculated ⁵ (1.5 g/l)</td>
</tr>
<tr>
<td></td>
<td>5,510 Pa·m³/mol</td>
<td>Zheng et al, 1997</td>
</tr>
<tr>
<td></td>
<td>5,217 Pa·m³/mol</td>
<td>Chang and Criddle, 1995</td>
</tr>
<tr>
<td>Flash point (closed cup), flammability limits at 20 - 25°C</td>
<td>None ⁵</td>
<td>ICI, 1993</td>
</tr>
<tr>
<td>Explosion limits in air at 1,013 hPa, at ambient temperature</td>
<td>None ⁵</td>
<td></td>
</tr>
<tr>
<td>Auto-flammability, ignition temperature</td>
<td>&gt; 743°C</td>
<td>Du Pont, 2002</td>
</tr>
</tbody>
</table>

- Reported as 5.7 bar
- Reported as 96 psia (pounds/inch²)
- Measured
- Calculated using the correlation log Kₗₒₚ = 0.10 + 0.81 × log Kₗₒₚ given for hydrophobic substances by Sabljic et al (1995), starting from the experimental value of log Kₗₒₚ = 1.06
- Molecular mass × 1 atm/solubility in water at 1 atm
- However, HFC-134a can become combustible under certain circumstances, e.g. at high temperatures/pressures and in oxygen-enriched air

Typically, commercial HFC-134a has a purity of ≥ 99.9%. Trace level impurities may include propylene, fluoroethane, methane and various halogenated hydrocarbons, depending on the conditions of the production process (Section 3.1).
2.4 Conversion factors

Conversion factors for HFC-134a concentrations in air at 25°C and 1,013 hPa are:

- 1 ppm = 4.169 mg/m³
- 1 mg/m³ = 0.240 ppm

In this report, converted values are given in parentheses.

The generic formula, from which the conversion factors for vapour concentrations in air are derived, is given in Appendix C. According to European standard conditions (20°C and 1,013 hPa) these would be: 1 ppm = 4.240 mg/m³ and 1 mg/m³ = 0.236 ppm.

2.5 Analytical methods

A method for the analysis of HFC-134a in air has been described. It is based on gas chromatography with flame ionisation detection. Resolution was achieved using a 0.1% SP1000 on 80-100 mesh Carbopack C glass column. The detection limit was 100 ppm (417 mg/m³) or lower (Hext, 1989).
3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

There are many possible processes for the manufacture of HFC-134a (Webb and Winfield, 1992). The main commercial processes include:

- hydro-fluorination of trichloroethylene, via 1-chloro-2,2,2-trifluoroethane (HCFC-133a);
- isomerisation/hydro-fluorination of 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113) to 1,1,-dichloro-1,2,2,2-tetrafluoroethane (CFC-114a) followed by hydro-dechlorination of the latter;
- hydro-fluorination of tetrachloroethylene to 1-chloro-1,2,2,2-tetrafluoroethane (HCFC-124) and subsequent hydro-dechlorination to HFC-134a.

Production of HFC-134a began by 1990 and from 1992 to 1999 there was a steady increase in annual quantity produced by industrial companies covered by the Alternative Fluorocarbons Environmental Acceptability Study (AFEAS) (McCulloch et al., 2003). For 1999, 2000, 2001 and 2002, production volumes reported to AFEAS were 134, 132, 136 and 159 kt, respectively (AFEAS, 2004).

3.2 Storage

HFC-134a (liquefied) is stored in cylinders and drums equipped with pressure relief valves. The cylinders should be kept in a clean, dry, well-ventilated area at temperatures preferably below 45°C. However in hot climates this temperature can be exceeded, and, as a result, drums and cylinders are tested at a reference temperature of 65°C. Storage vessels should be kept away from open flames, direct sunlight and all other sources of heat. Bulk installations are equipped with pressure relief systems, and storage temperatures are subject to the regulations of the territory. HFC-134a will form HF at elevated temperatures, such as those found in fire conditions.

HFC-134a is incompatible with finely divided metals, magnesium and alloys containing > 2.0% magnesium. It can react violently if in contact with alkali metals and alkaline earth metals such as sodium, potassium and barium (Ineos, 2002).

3.3 Transport and handling

HFC-134a may be shipped under US-DOT regulations using UN number 3159 hazard class 2.2, non-flammable gas or in Europe under ADR/RID hazard class 2A. Under ADR/RID (and UK) regulations, the maximum quantity per transport unit for any non-toxic, non-flammable liquefied
gas is 1,000 kg. In the USA, there are no specified limits for the bulk transport of HFC-134a by road or rail. The limit in one package for transport in a passenger plane or train is 75 kg and for a cargo plane is 150 kg (US Code of Federal Regulations).

In Germany, HFC-134a is classified as a low hazard to waters (Wassergefährdungsklasse WGK 1) (Umweltbundesamt, 2003).

3.4 Use

HFC-134a was developed as a substitute for fully halogenated chlorofluorocarbons and for partially halogenated hydrochlorofluorocarbons. Its main applications are in refrigeration and air conditioning (domestic, automotive and industrial), in which it is used either alone or as a component of blends.

Other applications are as a blowing agent for polyurethane foams and as a propellant for medical aerosols ("metered-dose inhalers").
4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

The environmental fate and impact of HFC-134a have been extensively reviewed in different scientific assessments on ozone depletion and climate change (WMO 1995, 1998; IPCC, 1995, 2001).

4.1 Emissions

4.1.1 Natural sources

There is no known natural source of HFC-134a.

4.1.2 Emissions during production and use

Atmospheric emissions of HFC-134a have risen steadily since 1990. In the years 1999, 2000, 2001 and 2002, estimated emissions were 69.8, 85.3, 95.0 and 106.9 kt, respectively (McCulloch et al., 2003; AFEAS, 2004). These emissions are mainly related to the use of HFC-134a in refrigerated transportation and automotive air conditioning.

4.2 Environmental distribution

The environmental partitioning of HFC-134a has been assessed (Franklin, 2003) using the equilibrium criterion (EQC) Level I and Level III models (Mackay et al., 1996).

In the Level I model, a fixed quantity of a supposedly non-degradable chemical is introduced into a closed evaluative environment and equilibrium achieved between the various environmental compartments (air, water, soil, sediment). The Level III model simulates a situation in which a chemical is emitted at a constant rate into one or more of the compartments, in each of which it may degrade; the steady-state distribution between compartments is then calculated. Due to the resistance to mass transfer between compartments, the various phases are not in equilibrium and the steady-state partitioning depends on its "mode of entry", i.e. the compartment(s) into which the chemical is injected.

EQC modelling has been performed for HFC-134a using the physical properties given in Table 1 and an atmospheric lifetime of 14.0 years, corresponding to a half-life of 9.7 years (Section 4.3.1). Degradation in other media was not taken into account. Table 2 below gives the percentage of HFC-134a calculated for each compartment.
The Level III simulation with emissions of HFC-134a to air alone leads to a distribution close to the Level I equilibrium situation as far as the air and water compartments are concerned. However, a much greater steady-state proportion of HFC-134a is found in the water compartment when the emissions are to water alone. This is due to the resistances to inter-media transfer (in particular from water to air) introduced in the Level III model.

Thus, HFC-134a released to air would remain almost exclusively in that compartment and, when released to water, would be expected to partition ultimately partition predominantly to the ambient air. Moreover, any HFC-134a present in surface or ground waters would have little tendency to partition to biota or soil as explained in Section 4.3.5 and 4.3.7.

### 4.3 Environmental fate and biotransformation

#### 4.3.1 Atmospheric fate and impact

*Lifetime*

The atmospheric degradation of HFC-134a occurs mainly in the troposphere, initiated by reaction with naturally occurring hydroxyl radicals (•OH) (photo-oxidation), and in the stratosphere through photolysis and reaction with O(1D) and OH. Both tropospheric and stratospheric degradation processes were taken into account to calculate an overall atmospheric lifetime of 14 years (IPCC, 1995), corresponding to a half-life of 9.7 years. More recent estimations remained very close to this value, i.e. 13.6 years (WMO, 1998), 13.8 years (IPCC, 2001) or 14.0 years (WMO, 2002).

The atmospheric lifetime of HFC-134a is much longer than either the intra- or inter-hemispheric mixing times. As a consequence, HFC-134a will become more or less uniformly distributed in the

---

* Lifetime is the time necessary for 63% degradation; it is equal to "half-life" divided by \( \ln 2 \) (= 0.69)
atmosphere on a global scale (Franklin, 1993). This conclusion is supported by atmospheric measurements (Section 5.1).

**Ozone depleting potential**

Since HFC-134a contains neither chlorine nor bromine, its ozone depletion potential (ODP) has generally been assumed to be zero (WMO, 1989; WMO, 1991).

The possibility of ozone depletion by CF₃Oₓ radicals (x = 1 or 2), arising from the atmospheric degradation of HFC-134a and other compounds, has been extensively studied. The results of these studies show that any contribution of CF₃Oₓ to ozone depletion is insignificant (Ko et al, 1994; Ravishankara et al, 1994) and that the ODP of HFC-134a is in any case expected to be less than 5 × 10⁻⁴. Semi-empirical methods and model calculations indicate values of less than 1.5 × 10⁻⁴ (the ODP of trichlorofluoromethane [CFC-11] = 1, for reference) (WMO 1995, 1998).

**Global warming potential**

The global warming potential (GWP) is the time-integrated radiative forcing resulting from emission to the atmosphere of a unit mass of a given substance, divided by the same quantity calculated for a reference substance. The radiative forcing is the additional earthward infrared radiation flux arising from the presence of the substance in the atmosphere. The GWP is calculated for a given "integration time horizon" (ITH). Depending on the reference substance, the ITH may be chosen to be finite (e.g. CO₂) or infinite (e.g. CFC-11).

Initially, the GWP of HFC-134a was calculated to be about 0.3 using CFC-11 as a reference and based on the atmospheric lifetime of 14 years (above) (Ko et al, 1993). Since then, the climate change issue has developed and the current, widely accepted method for calculating GWPs is to use CO₂ as a reference with a standard ITH of 100 years. The use of a finite ITH is needed in the case of CO₂ because when it is emitted to the atmosphere its disappearance cannot be described by a simple first-order decay of its atmospheric concentration and a residual concentration remains present. The generally accepted GWP (with ITH of 100 years) for HFC-134a has remained constant at 1,300 compared to CO₂ (= 1) since 1995 (IPCC, 1995, 2001).

The GWP gives an indication on a mass basis of the relative impact of a substance compared to CO₂. For several reasons, the GWP concept has been criticised (Académie des Sciences, 1994). Most importantly, the GWP, when used in isolation, does not measure the impact of a substance on the greenhouse effect, which depends on its real atmospheric concentration. The actual contribution of a greenhouse gas due to anthropogenic emissions can be calculated on the basis of
the radiative forcing due to the increase of atmospheric concentration of these species since pre-industrial times, as follows.

The atmospheric concentration of HFC-134a was reported to be on average 13.6 ppt in 2000 (Hall et al., 2002) (Section 5.1). Using a radiative efficiency of 0.15 W/m²·ppb (IPCC, 2001), this corresponds to a radiative forcing of 0.002 W/m². When compared with the radiative forcing due to CO₂ of about 1.46 W/m² (IPCC, 2001), the contribution of HFC-134a represents 0.14% of the contribution of CO₂. Projected contributions of HFC-134a to the greenhouse effect show that, even in the case of "scenario A1b" (IPCC, 2001), which tends to overestimate emissions of hydrofluorocarbons, the radiative forcing produced by HFC-134a would amount to 0.08 W/m² in 2050, i.e. increase 40-fold. Whereas the other main greenhouse gases would then contribute to 4.65 W/m², the relative radiative forcing of HFC-134a would still be minimal at about 1.7%.

In conclusion, although HFC-134a presently contributes insignificantly to the greenhouse effect, its contribution is expected to increase over the next decades.

Tropospheric ozone formation

Tropospheric ozone is an environmental issue due to its toxicity to humans and vegetation, and also its contribution to the greenhouse effect. The contribution of a substance to the formation of tropospheric ozone depends on its atmospheric reactivity. The greater a substance's reactivity with OH, the more it indirectly produces ozone close to its emission source. The mechanism of ozone formation involves the oxidation of NO to NO₂ by peroxy radicals resulting from the oxidation process and further photolysis of NO₂ to NO and O, the latter reacting with oxygen to form ozone.

HFC-134a, as illustrated by its atmospheric lifetime of 14 years (above), reacts very slowly and therefore has a negligible impact on ground ozone formation. A photochemical ozone creation potential has been calculated for this species by Hayman and Derwent (1997), with a value of 0.1 to be compared with the reference (ethylene = 100).

Degradation mechanism and products

Extensive consideration has been given to the atmospheric degradation scheme of HFC-134a since 1989 (WMO, 1989) and thereafter in many studies reported in the UNEP (United Nations Environment Programme) scientific assessment of ozone (WMO, 1991, 1995, 1998). The mechanism of atmospheric degradation of HFC-134a has been reviewed by Franklin (1993). Support for the basic reaction scheme proposed by WMO (1989) has been provided by laboratory
studies (see, for example: WMO, 1991; Edney and Driscoll, 1992; Tuazon and Atkinson, 1993; STEP/AFEAS, 1993) (Figure 1).

**Figure 1: Tropospheric degradation mechanism for HFC-134a**

- CF<sub>3</sub>-CH<sub>2</sub>F → HFC-134a → CF<sub>3</sub>-CHF<sup>+</sup> + •OH → H<sub>2</sub>O
- CF<sub>3</sub>-CHF → + O<sub>2</sub>
- CF<sub>3</sub>-CHFO<sub>2</sub>NO<sub>2</sub> → + NO<sub>2</sub> (hv or Δ)<br>- NO<sub>2</sub> (hv)
- CF<sub>3</sub>-CHFO<sub>2</sub>H → + NO – NO<sub>2</sub> + ‘OH (hv)
- CF<sub>3</sub>-CHF → + O<sub>2</sub> – HO<sub>2</sub>•
- Formyl fluoride: HC(O)F + CF<sub>3</sub>•<br>- HC(O)OH + HF → Formic acid
- CF<sub>3</sub>O<sub>2</sub>NO<sub>2</sub> → + NO<sub>2</sub> (hv or Δ)<br>- NO<sub>3</sub> (hv)
- CF<sub>3</sub>O<sub>2</sub>H → + NO – NO<sub>2</sub> – ‘OH (hv)
- CF<sub>3</sub>O • → + RH – R•
- CF<sub>3</sub>OH → CO<sub>2</sub> + HF → C(O)F<sub>2</sub> + HF

* NO<sub>3</sub>, NO<sub>2</sub> and NO<sub>3</sub>, free radicals
Breakdown of HFC-134a in the troposphere will be initiated by the •OH and will proceed via various intermediates to give the CF₃CHFO radical, which can either react with oxygen to form trifluoroacetyl fluoride (CF₃COF) or undergo carbon-carbon cleavage to give formyl fluoride (HCOF) and the CF₃ radical. The latter will ultimately be converted to carbonyl fluoride (COF₂) and HF. Earlier atmospheric modelling studies predicted that, as an average over the whole troposphere, about 40% of HFC-134a would be converted to CF₃COF and 60% to HCOF + COF₂ + HF. But these results were based on the yield of trifluoroacetyl fluoride obtained in the previous laboratory studies which were made in the absence of NOₓ. In the presence of NOₓ, as is the case in real atmospheric conditions, it was shown that the yield of trifluoroacetyl fluoride ranges from 7 to 20%, i.e. not as high as in previous observations (Wallington et al, 1996).

A theoretical explanation of this effect has been proposed by Wallington et al (1996) on the basis that the formation of the alkoxy radical of HFC-134a by reaction of the corresponding peroxy radical with NO is exothermic (ΔH = –17 kcal/mol) whereas the reaction of two peroxy radicals used in previous experiments to form alkoxy radicals is almost thermoneutral. In the presence of NOₓ, the formation of vibrationally excited alkoxy radicals resulting from this reaction is an explanation of an easier carbon-carbon bond cleavage and thus less formation of trifluoroacetyl fluoride through reaction with oxygen. Following those observations the accepted yield of trifluoroacetyl fluoride from HFC-134a atmospheric decomposition was closer to 15% than to the previously proposed 40%.

Although peroxynitrites (CF₃CHFO₂NO₂, CF₃O₂NO₂), hydroperoxides (CF₃CHFO₂H, CF₃O₂H) and trifluoromethanol (CF₃OH) may be formed during the degradation, they are thought to be short-lived intermediates.

The principal fate of the acid fluorides (CF₃COF, HCOF and COF₂) will be uptake by cloud water with an estimated atmospheric lifetime of 70 days assuming that carbonyl halides behave closely enough to phosgene for which this calculation was done (WMO, 1998), followed by hydrolysis to trifluoroacetic acid (TFA), formic acid (HCOOH), CO₂ and HF. Dry deposition of the acid fluorides to ocean or land surfaces may occur to a limited extent; it will in any case be followed by hydrolysis (AFEAS, 1992; STEP/AFEAS, 1993).

4.3.2 Environmental impact of atmospheric degradation products of HFC-134a

Contribution to acid rain and environmental burden of fluoride ion

On the basis of 15% conversion of HFC-134a to TFA and HF, 85% conversion to HCOOH, CO₂ and HF, and uniform scavenging of the acids thus produced into the global average rainfall of
$5 \times 10^{11}$ kt/y, the calculated resulting levels of fluoride and acidity are low compared with those arising from existing sources:

Assuming steady state conditions with an atmospheric release and degradation rate of 100 kt HFC-134a/y (equal to the expected releases in the early part of this century):

- F$^-$ production would be 66 kt/y, i.e. very small compared with the estimated atmospheric fluoride flux of 1,000 to 8,000 kt/y (WMO, 1989);
- the contribution of HFC-134a to the F$^-$ concentration in rainwater would be 0.12 µg/l. This level should be compared with typical fluoride concentrations in "background" rainwater of around 10 µg/l, i.e. 100 times greater, and with levels of about 1 mg/l used for the fluoridation of drinking water, i.e. 10,000 times greater (WMO, 1989);
- the trifluoroacetic, formic and hydrofluoric acids formed from HFC-134a and scavenged in rainwater would represent an acidity of $4.46 \times 10^9$ mol H$^+$/y, i.e. about 3,000 times less than the acidity arising from natural and anthropogenic emissions of SO$_2$ and NO$_x$ (UKRGAR, 1990; Galloway, 1995). Thus the contribution of HFC-134a to acid rain would be negligible.

### 4.3.3 Contribution of HFC-134a to environmental trifluoroacetic acid

A complete risk assessment has been conducted on TFA, indicating that no environmental impact is expected from TFA produced by the atmospheric degradation of HFC-134a and other known precursors of TFA (Boutonnet et al, 1999).

The atmospheric wet deposition rates of TFA due to HFC-134a are fairly small due to its low atmospheric concentration (Section 5.1). This source in addition to other HCFC precursors cannot explain observed rainwater concentrations ranging between 3 and more than 200 ng/l and open sea concentrations. Large natural sources of TFA would also be needed to explain the relatively high concentrations of TFA (typically around 200 ng/l) found in the open ocean, both at the surface and in deep ocean water. It is therefore concluded that TFA is a naturally occurring chemical in the environment. The amount present in the oceans was estimated to be 268 Mt. The amount of TFA that would be produced from degradation of HFC-134a on the basis of the assumptions made in Section 4.3.1 would be 15 kt/y, which is considered to be negligible compared to the existing amounts (Frank et al, 2002).

Making the same assumptions as in Section 4.3.1 for the future emission and degradation rates of HFC-134a, its conversion to TFA and the incorporation of the latter into rainwater, one can calculate that:

- the amount of TFA formed would be on average about 15 kt/y;
- the corresponding concentration of TFA in precipitation due to HFC-134a degradation would be about 33 ng/l;
- if all the TFA accumulated in the upper mixed layer of the oceans, there would be a resulting seawater TFA concentration increase of about 0.5 ng/l per 100 kt HFC-134a degraded. This remains negligible in comparison with the natural background.

The physico-chemical properties of TFA indicate that it will partition into the aqueous compartments of the environment, where it will be completely ionised, showing no appreciable tendency to adsorb onto soils or to accumulate passively in biota.

In the aqueous phase several possible abiotic processes have been reviewed in Boutonnet et al (1999) including heterogeneous photocatalytic processes or reaction with reactive species formed through natural photolytic processes (e.g. 'OH, RO₂⁻), with no significant rates of degradation observed or expected because of the small concentration of reactive species. In some cases reaction rate was measured but was found to be very slow, e.g. in the case of oxidation by NO₃ radicals in atmospheric clouds followed by decarboxylation with a corresponding half-life of 80 years.

In the gas phase, the reaction with 'OH is significant with a rate constant of 0.12 × 10⁻¹² cm³/molecule/s corresponding to a globally averaged half-life of 66 days (Carr et al, 1994). Since TFA stays preferentially in the aqueous phase and is rained out with a half-life of the same order, only a part of TFA will be degraded through that process. In fact, for the free acid TFA (rather than for its precursor CF₃COF), rain-out is likely to be faster. Thus, Rodriguez et al (1991) estimated lifetimes of around 12 and 10 to 30 days for rain-out and surface uptake, respectively (corresponding to half-lives of 8 and 7 to 21 days). So reaction with OH is likely to be a minor sink for TFA.

### 4.3.4 Aquatic fate

Any HFC-134a which might be present in aqueous waste streams discharged directly into rivers or lakes would be expected, by analogy with similar compounds, to have a half-life with respect to volatilisation of several days to a few weeks. A calculation with EpiWin software (US-EPA, 2003) suggests volatilisation half-lives of about 1 hour for rivers and 96 hours for lakes (Libre, 2003).

### 4.3.5 Terrestrial fate

No data are available.
The log $K_{oc}$ may be estimated to be 0.96 (Table 1), which indicates that HFC-134a has only a moderate sorption affinity to soil from aqueous media and would therefore be expected to be mobile in soil.

### 4.3.6 Biodegradation

In the closed bottle assay with activated sludge, there was negligible (2 to 3%) biodegradation of HFC-134a after 28 days (Tobeta, 1989). Under laboratory conditions, aerobic degradation by the methanotrophic bacterium *Methylosinus trichosporium* OB3b was also unsuccessful (DeFlaun *et al.*, 1992).

Studies reviewed by Boutonnet *et al* (1999) did not show any reproducible biodegradation of TFA. More recent work showed TFA to be co-metabolically biodegraded under anaerobic conditions (Kim *et al.*, 2000). However, although this work suggests a potential for TFA biodegradation under specific conditions, it does not indicate to what extent it will take place in the real environment and, if so, at what disappearance rate.

### 4.3.7 Bioaccumulation

No data are available.

The log $K_{ow}$ is 1.06 (Table 1), indicating the absence of any significant potential for passive bioaccumulation (PAFT, 1990).
5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

Since production of HFC-134a began in the early 1990s, the atmospheric background concentrations of HFC-134a have risen steadily from levels close to zero, with measurements taken between 2000 and 2002 indicating values generally in the range 10 to 30 ppt, depending on latitude and time of sampling (Hall et al, 2002; WMO, 2002; AGAGE, 2003). The average growth rate since 1998 has been 3.2 to 3.5 ppt/y (Hall et al, 2002; WMO, 2002). There is good agreement between observed concentrations and those calculated on the basis of estimated emissions (McCulloch et al, 2003).

5.2 Human exposure levels and hygiene standards

5.2.1 Non-occupational exposure

Consumer exposure has not been measured directly.

5.2.2 Occupational exposure

No published sources of industrial hygiene monitoring data are available.

5.2.3 Hygiene standards

The American Industrial Hygiene Association's Workplace Environmental Exposure Level Committee (WEEL) has assigned HFC-134a an occupational exposure limit of 1,000 ppm (4,170 mg/m³) as an 8-h time-weighted-average concentration. This is the highest level given for substances of very low toxicity and is based on the good house-keeping principle that exposures to all substances except CO₂ should be maintained at or below 1,000 ppm (AIHA, 1991). The German MAK Commission have also set an occupational exposure limit of 1,000 ppm (8-hour TWA) for HFC-134a (Greim, 2004), as have a number of other national occupational exposure standard setting bodies (Table 3).
### Table 3: Occupational exposure limit values

<table>
<thead>
<tr>
<th>Country</th>
<th>TWA (ppm)</th>
<th>STEL (mg/m³)</th>
<th>STEL (ppm)</th>
<th>STEL (mg/m³)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>1,000</td>
<td>4,200</td>
<td>4,000 b</td>
<td>16,800 b</td>
<td>DFG, 2003</td>
</tr>
<tr>
<td>Germany</td>
<td>1,000</td>
<td>4,200</td>
<td>4,000 b</td>
<td>16,800 b</td>
<td>TRGS, 2003</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1,000</td>
<td>4,200</td>
<td>-</td>
<td>-</td>
<td>Gezondheidsraad, 2003</td>
</tr>
<tr>
<td>Sweden</td>
<td>500</td>
<td>2,000</td>
<td>750</td>
<td>3,000</td>
<td>Arbetarskyddstyrelsen, 2000</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1,000</td>
<td>4,200</td>
<td>-</td>
<td>-</td>
<td>SUVA, 2003</td>
</tr>
<tr>
<td>UK</td>
<td>1,000</td>
<td>4,420</td>
<td>-</td>
<td>-</td>
<td>HSE, 2002</td>
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<tr>
<td>USA</td>
<td>1,000</td>
<td>4,200</td>
<td>-</td>
<td>-</td>
<td>AIHA, 1991</td>
</tr>
</tbody>
</table>

TWA: Time-weighted average concentration (8-h working period)
STEL: Short-term exposure limit (15 min, unless specified otherwise)

* Official values; some countries use different molar volume and/or other ambient temperature

b Maximum 4 ×/shift

The US Acute Exposure Guideline Level (AEGL) committee has developed recommended guideline levels for HFC-134a for accidental exposures lasting from 10 minutes to up to 8 hours. The AEGL-1, a level that should not cause any adverse effects, is 8,000 ppm (33,400 mg/m³). This is based on the rapid uptake and equilibration of HFC-134a in the body (approximately 50 minutes); the absence of chronic effects in animals (Section 8.3) and results of a clinical study in which human subjects were exposed to levels up to 8,000 ppm for 1 hour without any effects (Chapter 9). The AEGL-2, a level that could represent a conservative threshold for serious toxicity, is 13,000 ppm (54,200 mg/m³). This is based on the no-observed effect level (NOEL) in a highly sensitive cardiac sensitisation study using dogs given injections of adrenaline (epinephrine) with simultaneous exposure to HFC-134a at 40,000 ppm (167,000 mg/m³) (Section 8.1.2). The AEGL-3, a level that could represent a conservative threshold for lethality, is 27,000 ppm. This is based on the threshold level for cardiac effects in the same highly sensitive cardiac sensitisation study using dogs given injections of epinephrine with simultaneous exposure to HFC-134a at 80,000 ppm (334,000 mg/m³) (National Research Council, 2002).
6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Environmental testing of HFC-134a has only been carried out on aquatic organisms. As HFC-134a is a gas, special procedures were employed to obtain solutions of the test substance and to prevent losses occurring during the test. All exposure concentrations were analytically verified.

6.1 Bacteria

The 6-hour EC$_{10}$ for HFC-134a for growth inhibition of bacterium Pseudomonas putida was > 730 mg/l. No inhibition of growth was observed (Coleman and Thompson, 1990 – CoR 1b; Berends et al, 1999 – CoR 2a).

6.2 Invertebrate aquatic species

The 48-hour EC$_{50}$ for HFC-134a in Daphnia magna under static conditions was 980 mg/l. A steep concentration/immobility curve was observed, mean measured concentrations of 870 and 1,100 mg/l causing 0 and 100% immobility respectively (Stewart and Thompson 1990 – CoR 1b; Berends et al, 1999 – CoR 2a).

6.3 Fish

The 96-hour LC$_{50}$ for HFC-134a in rainbow trout (Salmo gairdneri) was 450 mg/l under semi-static conditions. No mortality was observed at concentrations of 180 and 300 mg/l, although symptoms of toxicity were observed (dark discolouration, quiescence and sounding behaviour). No symptoms of toxicity were seen at a concentration of 87 mg/l (Thompson, 1990 – CoR 1b; Berends et al, 1999 – CoR 2a).

6.4 Summary and evaluation

The available studies in bacteria, invertebrates and fish indicate that HFC-134a has a very low acute toxicity to aquatic organisms. Furthermore, due to its low octanol/water partition coefficient (log K$_{ow}$ = 1.06; Table 1), HFC-134a is unlikely to bioaccumulate.
7. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION

7.1 In vivo

Male and female Wistar rats were exposed to atmospheres containing 10,000 ppm (41,700 mg/m³) ¹⁴C-labelled HFC-134a for a period of 1 hour. On cessation of exposure, the animals were removed from the inhalation chambers and housed individually in glass metabolism cages. Urine and faeces were collected, as well as expired organic material and carbon dioxide. The total radioactivity measured in expired air, urine and faeces amounted to approximately 1% of the inhaled dose in both male and female rats. This represented the amount of the inhaled dose of HFC-134a that had been absorbed. Of this 1% of radioactivity, approximately 0.67% was exhaled within 1 hour after cessation of exposure as unchanged HFC-134a. The half-life of excretion of HFC-134a was of the order of 20 minutes. The remaining radioactivity (approximately 0.33%) was excreted in the first 24 hours after cessation of exposure. Carbon dioxide, seen in exhaled air, was the major metabolite, accounting for 0.22% of the inhaled dose of HFC-134a for male and 0.27% for female rats. Urinary excretion accounted for 0.09% of the inhaled dose in both sexes and faecal excretion accounted for 0.04%. A single metabolite was detected in the urine by ¹⁹F-nuclear magnetic resonance (NMR) spectrometry; it was identified as TFA. Total metabolism, measured as the sum of radioactivities in urine, faeces and as carbon dioxide was 0.34% and 0.40% of the inhaled dose of HFC-134a in males and females, respectively. Analyses of a range of tissues at the end of the study showed a relatively uniform distribution of radioactivity. There was no evidence for specific accumulation in any organ or tissue, including fat (Ellis et al., 1991, 1993; CoR 1a).

A clinical study was conducted in human volunteers (4 males and 4 females) exposed to levels of 1,000 to 8,000 ppm HFC-134a (4,170 - 33,400 mg/m³) for 1 hour. The concentrations of HFC-134a in the blood increased rapidly and in an exposure-dependent manner. The concentrations approached steady state within 30 minutes and tended to be higher in males than females. The mean maximum blood concentrations following exposure to 8,000 ppm HFC-134a were 6.0 and 7.2 µg/ml, in females and males respectively and were achieved within 30 to 55 and 55 minutes of commencement of exposure, in females and males respectively. Following the end of the exposure period, blood concentrations declined rapidly, predominantly in a bi-phasic manner and independent of exposure concentration. The α-elimination half-life was less than 11 minutes, while the β-elimination half-life was 42 minutes. The mean residence time was 44 minutes (Emmen et al., 2000; CoR 1a).

Rats were exposed to concentrations of 2,500, 10,000 or 50,000 ppm (10,400, 41,700 or 208,000 mg/m³) HFC-134a for 1 hour. The substance was rapidly absorbed and blood levels reached a plateau in 15 minutes. The peak blood levels were 7.9, 18.1 and 66.0 µg/ml

[^a]: Equivalent to amount of fluorocarbon available for absorption in the respiratory tract over exposure period of 1 hour.
respectively. When exposure ceased, the blood levels declined rapidly with an estimated half-life of between 4 and 7 minutes. A second, slower elimination phase accounted for a minor proportion of the overall absorbed dose. There was no marked sex difference in the kinetics of HFC-134a and there was no evidence of any accumulation in rats (Alexander and Libretto, 1995; CoR 1d).

Dogs were exposed to HFC-134a either by inhalation for 1 hour at a concentration of 120,000 ppm (500,000 mg/m³) or by the instillation into the lung of metered doses of 0.45, 1.5 or 4.5 g/d by oropharyngeal tube. Typical mean blood concentration of 159 µg/ml (following inhalation) and 14.6, 21.2 and 31.8 µg/ml following metered doses, respectively, were achieved (Alexander and Libretto, 1995; CoR 1d).

HFC-134a has been shown to cross the placental barrier in both rats and rabbits (Alexander and Libretto, 1995).

Male Wistar-derived rats (Alderley Park strain) were exposed to atmospheric concentrations of 10,000, 25,000 or 50,000 ppm HFC-134a (41,700, 104,000 or 208,000 mg/m³) for up to 6 hours. Blood levels of HFC-134a were monitored and urine, plasma and the testes were analysed using ¹⁹F-NMR spectroscopy for fluorinated metabolites, which were identified and quantified. Steady-state blood levels of HFC-134a were achieved within 2 hours and were 25.1, 52.2 and 102.9 µg/ml, respectively. Three urinary metabolites were identified; trifluoroethanol (TFEth) as the aglycone and the glucuronide, trifluoroacetaldehyde (TFAA) as its hydrate and urea adduct, and trifluoroacetic acid (TFA). These metabolites were also identified in the plasma and, to a lesser extent, testicular tissue. The blood:air partition coefficient for HFC-134a was 0.48 as measured under physiological conditions (Ellis, 1996 – CoR 1d; Green et al, 1996 – CoR 4a).

7.2 *In vitro*

The metabolism of HFC-134a was studied in rat liver microsomal incubates exposed to HFC-134a. ¹⁹F-NMR spectroscopic analysis identified both TFAA and TFA as metabolites of HFC-134a. The metabolism of TFAA was also studied using rat and human liver microsomes and rat liver cytosol. Both TFEth and TFA were identified as metabolites using ¹⁹F-NMR spectroscopy, with TFEth being the major metabolite in rat liver cytosol, where saturable metabolism was demonstrated. There were no significant differences in the rates of metabolism of HFC-134a in rat and human liver microsomes. Defluorination of both TFAA and TFEth, but not TFA, was also demonstrated in rat liver microsomes. The metabolite profile is consistent with an oxidative route of metabolism for HFC-134a (Ellis, 1996; CoR 1d).
Studies on the metabolism of HFC-134a in isolated rat hepatocytes have shown that the molecule undergoes limited metabolism as measured by the release of inorganic fluoride. The amount of defluorination is proportional to the headspace concentration of HFC-134a. With 50% HFC-134a in the head-space, fluoride release amounted to 12 mmol fluoride/mg protein in 2 hours. The microsomal metabolism was inhibited by carbon monoxide, was decreased in the presence of low oxygen concentration, and was increased in the presence of hepatic microsomes isolated from Arochlor-treated rats. These results indicated that HFC-134a undergoes a cytochrome P450-catalysed defluorination reaction (Reidy et al, 1990; CoR 2e). Olson et al (1990; CoR2e) concluded that the cytochrome P450-dependent oxidation of HFC-134a is catalysed primarily by P450IIE1. In vitro oxidative defluorination was demonstrated in rat, rabbit and human liver microsomes resulting in inorganic fluoride and TFA. Specific activity of cytochrome P450IIE1 in humans is similar to animals.

Harris et al (1992; CoR 2e) found no evidence of trifluoroacetylated proteins in rats exposed to 10,000 ppm HFC-134a (41,700 mg/m³) for 6 hours, indicating that metabolism does not involve a trifluoroacetyl halide.

### 7.2.1 Physiologically-based pharmacokinetic modelling

The quantitative data generated in the study by Ellis (1996) (Section 7.1) have been used to construct a physiologically-based pharmacokinetic model to predict the uptake and metabolism of HFC-134a in rats and humans. The model was used to simulate the blood levels of the HFC metabolite, trifluoroacetaldehyde (TFAA), in humans exposed to HFC-134a in a variety of scenarios. For example, the blood levels of TFAA in humans resulting from exposure to HFC-134a from a metered dose inhaler application (0.023 μg/l) or as a consequence of a leak in an automobile air conditioning unit (4.8 μg/l) were predicted to be at least 34 times lower than the blood levels of TFAA in the rat exposed to HFC-134a at its NOAEL of 10,000 ppm (41,700 mg/m³) for 6 hours (163.0 μg/l) (Green et al, 1996; CoR 2e).

### 7.3 Summary

HFC-134a is rapidly absorbed and equilibrated in tissues after inhalation and is eliminated from the blood in expired air with a half-life of a few minutes. Metabolism to TFA occurs only in minor amounts.
8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

No specific oral and dermal toxicity data are available (HFC-134a is a gas at room temperature).

8.1 Single exposure

HFC-134a is of low acute toxicity by the inhalation route. In the rat, a 15-minute LC$_{50}$ of > 800,000 ppm (3,340,000 mg/m$^3$) and a 4-hour LC$_{50}$ of > 500,000 ppm (2,080,000 mg/m$^3$) have been reported (Collins, 1990; CoR 4e).

An approximate 4-hour lethal concentration, the lowest concentration that produced death, of 567,000 ppm HFC-134a (2,360,000 mg/m$^3$) in the male ChR-CD rat (6/group) has been reported. In this study, mortalities were 0/6 at 81,100, 205,200 and 359,300 ppm (338,000, 855,000, 1,497,900 mg/m$^3$), 5/6 at 566,700 ppm (2,362,600 mg/m$^3$), 0/6 at 646,700 ppm (2,696,100 mg/m$^3$) and 2/6 at 652,700 ppm (2,721,100 mg/m$^3$). The range of measured concentrations in the 566,700 ppm group at which high mortality occurred was very wide, 494,400 to 668,800 ppm (2,061,200 - 2,788,200 mg/m$^3$), the highest concentration exceeding that of the second highest group 664,300 ppm (2,769,500 mg/m$^3$) and similar to the high end of the range for the highest concentration group at 685,300 ppm (2,857,000 mg/m$^3$). Clinical signs reported during the exposure included lethargy, laboured and rapid respiration, salivation and lachrymation (Silber, 1979a; CoR 2e).

HFC-134a was not lethal to dogs exposed by inhalation to a concentration of 700,000 or 800,000 ppm (2,920,000 or 3,340,000 mg/m$^3$) for 3 to 5 hours (Shulman and Sadove, 1967; CoR 2e).

A 10-minute EC$_{50}$ for anaesthetic effects, measured by the loss of the righting reflex, was 280,000 ppm (1,170,000 mg/m$^3$) in the rat (Ferguson-Smith, 1993; Tinston, 1976; both cited by Calm, 2000; CoR 4b) and 270,000 ppm (1,126,000 mg/m$^3$) in the mouse (Shulman and Sadove, 1967; CoR 2e).

Han-Ibm Wistar rats and B6C3F$_1$ mice were exposed (snout-only) for 1 hour to a concentration of 810,000 ppm HFC-134a (3,380,000 mg/m$^3$), with oxygen supplementation and to concentrations up to 150,000 ppm (625,000 mg/m$^3$) without oxygen supplementation. No deaths or treatment-related post mortem findings were reported in mice or rats killed either 3 or 15 days following exposure. Mice exposed to 150,000 ppm HFC-134a showed laboured respiration and female mice were comatose after 15 minutes exposure. Decreases in various respiratory parameters were reported in mice: in tidal volumes when exposed to 74,000 ppm (309,000 mg/m$^3$), in respiratory rate when exposed to 90,500 ppm (377,300 mg/m$^3$) and in respiratory minute volume when
exposed to 150,000 ppm. Respiratory rates were reduced in rats exposed to concentrations of 47,000 ppm HFC-134a (196,000 mg/m³) and above and tidal volumes were reduced in rats exposed to concentrations above 47,000 ppm. These observations were accompanied by small reductions in pO₂ and small increases in pCO₂, which were judged to be consistent with oxygen deprivation (Alexander and Libretto, 1995; CoR 1a).

Groups of 4 Beagle dogs were exposed to HFC-134a at concentrations up to 320,000 ppm (1,330,000 mg/m³) for 1 hour. No effects on body weight gain, food consumption, electrocardiography or post mortem findings were reported. There were no clinically related findings in dogs exposed to either 40,000 or 80,000 ppm HFC-134a (167,000, 334,000 mg/m³). Exposure to 160,000 ppm HFC-134a was poorly tolerated by 3 out of 4 dogs, which showed head shaking, salivation and struggling. The effects were more severe following exposure to 320,000 ppm, with only one dog in the group completing the full exposure (Alexander and Libretto, 1995; CoR 1a).

8.1.1 Narcotic potential

HFC-134a administered by inhalation induced anaesthesia in dogs, cats and monkeys within 1 minute of exposure at concentrations of 500,000, 600,000, 700,000 or 800,000 ppm (2,080,000, 2,500,000, 2,920,000 or 3,340,000 mg/m³) and above (there is no comment about O₂ supplementation in the original reference). In dogs, HFC-134a produced light anaesthesia at concentrations between 500,000 and 600,000 ppm, moderate anaesthesia from 600,000 to 700,000 ppm and deep anaesthesia from 700,000 to 800,000 ppm. Deep anaesthesia was characterised by rapid respiration, tachycardia and relaxation of abdominal muscles. In cats and monkeys HFC-134a concentrations in excess of 600,000 ppm were associated with respiratory depression. Emergence from deep anaesthesia generally occurred within 2 minutes post-exposure (Shulman and Sadove, 1967; CoR 2e).

8.1.2 Cardiac sensitisation

Early studies on the toxicity of certain hydrocarbons, especially anaesthetics, showed that they could render the mammalian heart abnormally reactive or sensitive to adrenaline (epinephrine) resulting in cardiac arrhythmias. HFC-134a has also been studied for this effect.

Male Beagle dogs were exposed to nominal HFC-134a concentrations of 50,000, 75,000 or 100,000 ppm (208,000, 313,000, 417,000 mg/m³) and given a bolus injection of 8 µl/kgbw epinephrine. Two of 10 dogs exposed to 75,000 ppm and 2 of 4 dogs exposed to 100,000 ppm exhibited a marked response (multiple extrasystoles). One dog exposed to 100,000 ppm
developed ventricular fibrillation and cardiac arrest. None of the 10 dogs exposed to 50,000 ppm HFC-134a exhibited a cardiac sensitisation response (Mullin, 1979; CoR 2e).

In another study in Beagle dogs, the cardiac sensitisation potential of HFC-134a was evaluated at concentrations of 40,000, 80,000, 160,000 or 320,000 ppm (167,000, 334,000, 667,000, 1,330,000 mg/m³) until equilibrium concentrations in the blood were established (after approximately 5 minutes of exposure). At that time, the dogs were given an intravenous injection of adrenaline (8 µg/kg) and monitored for cardiac arrhythmia. Three of 10 dogs exposed to 80,000 ppm developed cardiac arrhythmia, as did 4 out of 10 dogs exposed to 160,000 ppm and 3 out of 4 dogs exposed to 320,000 ppm. Concentrations of 40,000 ppm HFC-134a were tolerated without any signs of cardiac arrhythmia. The reference compound in this study, CFC-12 (dichlorodifluoroethane), showed a comparable cardiac sensitisation potential (Hardy et al, 1991; Brock et al, 2003).

### 8.2 Skin and eye irritation, sensitisation

#### 8.2.1 Skin irritation

Liquefied HFC-134a (0.5 ml per application site) was applied on to a square of 8 layers of thick gauze pads. The gauze pads were placed on scarified and intact skin areas of rabbits, covered with an occlusive polypropylene film and fixed with an adhesive tape. Slight irritation to intact skin, possibly due to local freezing, appeared after 24 hours of contact (Mercier, 1989; CoR 2e).

HFC-134a vapour (3.0 g) was applied directly onto guinea pig skin, twice daily, using a metered dose device. No signs of irritation were reported (Alexander and Libretto, 1995; CoR 1a).

#### 8.2.2 Eye irritation

Gaseous HFC-134a directed from a distance of 10 cm into the eyes of rabbits for 5 or 15 seconds resulted in very slight irritation (Mercier, 1990a; CoR 2e). This effect is possibly a physical consequence of the test procedure.

HFC-134a vapour (0.375 g) was applied (2 ×/d) directly into the rabbit eye, using a metered dose device. No signs of irritation were reported (Alexander and Libretto, 1995; CoR 1a).
8.2.3 Skin sensitisation

Guinea pigs received one single intradermal injection of Freund's complete adjuvant followed by 7 occlusive epicutaneous administrations of 0.5 ml of liquefied HFC-134a, which was applied to the occlusive bandage before it was put in place, every 2 or 3 days over a 15-day period. The treated occlusive bandage was left in place between each application. After a period of 12 days without treatment, the challenge administration was performed by occlusive epicutaneous treatment with 0.5 ml of liquefied HFC-134a. No evidence of skin sensitisation was observed (Mercier, 1990b; CoR 1b).

HFC-134a vapour (6.0 g) was applied directly onto guinea pig skin for 6 days, using a metered dose device. The exposed site was then re-challenged with a further dose of 6.0 g HFC-134a after a period of 6 days. It is reported that HFC-134a showed essentially no signs of contact sensitisation potential, although it is unclear whether one of the standard OECD skin sensitisation protocols was employed in this study (Alexander and Libretto, 1995; CoR 1a).

8.3 Repeated exposure

Male ChR-CD rats (10/group) were exposed (6 h/d, 5 d/wk) to 0 or 100,000 ppm (0, 417,000 mg/m³) HFC-134a for 14 days. At the end of exposure, 5 treated and 5 control rats were randomly selected and sacrificed for pathological evaluation. The remaining 5 rats per group were held for a 14-day recovery period. During the exposure, the animals showed an increased respiratory rate. No treatment-related abnormalities were observed with respect to body weight gain, haematology or blood chemistry. Analysis of the urine samples collected after the 9th exposure resulted in a significant increase in fluoride excretion in the treated rats, suggesting metabolism of HFC-134a. Organ weights of treated and control rats exhibited no significant differences and no compound-related pathological changes were observed in any of the exposed rats ( Silber, 1979b; CoR 1d).

Wistar-derived rats (Alderley Park strain) (16/sex/group) were exposed (6 h/d, 5 d/wk) to 0, 1,000, 10,000 or 50,000 ppm (0, 4,170, 41,700, 208,000 mg/m³) HFC-134a for 4 weeks. Evidence that the gas was absorbed into the blood during exposure was obtained. No treatment-related abnormalities were observed with respect to body weight, clinical signs, food intake and food utilisation, haematology, blood chemistry, urine composition or ophthalmoscopy. Increases in liver and kidney weights and decreases in gonad weights were noted. These changes were confined to male rats exposed to 50,000 ppm except for an increase in liver weight, which was also seen in those male rats exposed to 10,000 ppm. There were no pathological changes in these tissues and the liver and kidney weight increases are considered to be due to a physiological

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* Organisation for Economic Co-operation and Development
adaptation to treatment and not considered to constitute toxic responses to treatment. The reduced testicular weights are interpreted in the same manner and are, in the absence of morphological changes, not of toxicological significance. A slight focal interstitial pneumonia was the only pathological change noted in males exposed to 50,000 ppm HFC-134a which was possibly related to treatment (Riley et al, 1979; CoR 1a). These effects have not been seen in subsequent studies.

Sprague-Dawley rats (20/sex/group) were exposed (6 h/d, 5 d/wk) to concentrations of 0, 2,000, 10,000 or 50,000 ppm (0, 8,340, 41,700, 208,000 mg/m³) HFC-134a for 13 weeks. Ten males and 10 females from each group were killed in week 14 following the last exposure, and the remaining animals were killed in week 18 following a 4-week recovery phase. Small differences in body weight gain and food consumption were noted between treated and control animals but these are considered to be due to minor environmental differences in the holding chambers. There were no significant differences in blood or urine clinical chemistry parameters, haematology parameters, ophthalmoscopy or organ weights and no treatment-related macroscopic or microscopic pathology findings were reported (Hext, 1989; CoR 1a).

8.4 Genotoxicity and cell transformation

8.4.1 In vitro

The available data from in vitro studies are summarised in Table 4.
### Table 4: The genetic toxicity of HFC-134a in vitro

<table>
<thead>
<tr>
<th>Endpoint / Species</th>
<th>Strain</th>
<th>Protocol</th>
<th>Concentration (%)</th>
<th>Result</th>
<th>Remark</th>
<th>Reference</th>
<th>CoR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em></td>
<td>TA1535, TA1537, TA1538, TA98, TA100</td>
<td>Plate suspension (up to 1 h) or plate incorporation (24 h), 48 h incubation</td>
<td>100 (417)</td>
<td>−ve *</td>
<td>+/- S9</td>
<td>Brusick, 1976</td>
<td>2a</td>
</tr>
<tr>
<td></td>
<td>S. typhimurium</td>
<td>TA1535, TA1538, TA98, TA100</td>
<td>Plate incorporation (72 h), 72 h incubation</td>
<td>Up to 50 (208)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Longstaff et al, 1984</td>
</tr>
<tr>
<td></td>
<td>S. typhimurium</td>
<td>TA1535, TA1538, TA98, TA100</td>
<td>Plate incorporation, 24 and 48 h incubation</td>
<td>Up to 100 (417)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Callander and Priestley, 1990</td>
</tr>
<tr>
<td></td>
<td>S. typhimurium</td>
<td>TA1535, TA1538, TA98, TA100</td>
<td>Plate incorporation, 24 and 48 h incubation</td>
<td>Up to 60 (250)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Araki, 1991</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>WP2 uvrA</td>
<td>Plate incorporation, 24 and 48 h incubation</td>
<td>Up to 60 (250)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Araki, 1991</td>
<td>2a</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Not specified</td>
<td>Plate incorporation, 24 h incubation</td>
<td>Up to 100 (417)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Alexander and Libretto, 1995</td>
<td>1a</td>
</tr>
<tr>
<td><em>Saccharomyces cerevisiae</em></td>
<td>D4</td>
<td>Plate suspension (1 h) or incorporation (24 h), 48 h incubation</td>
<td>100 (417)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Brusick, 1976</td>
<td>2a</td>
</tr>
<tr>
<td><em>Mouse lymphoma</em></td>
<td>L51787</td>
<td>Plate incorporation, 4 h incubation</td>
<td>Up to 100 (417)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Alexander and Libretto, 1995</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Chromosome aberration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human lymphocytes</td>
<td>2 donors (3 h), 72 and 96 h incubation</td>
<td>Up to 75 (313)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Mackay, 1990</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Chinese hamster lung (CHL) cells</td>
<td>6 h (+S9), 24 and 48 h (−S9); 24 and 48 h incubation</td>
<td>40 - 100 (167 - 417)</td>
<td>−ve</td>
<td>+/- S9</td>
<td>Asakura, 1991</td>
<td>2a</td>
<td></td>
</tr>
</tbody>
</table>

*a* −ve, negative
Gene mutation in bacteria and yeast

HFC-134a has been tested in four separate Ames assays using Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, and Escherichia coli strain WP2 uvrA. In all cases, HFC-134a was shown to be non-mutagenic, both in the presence and absence of S9\(^a\) metabolic activation (Brusick 1976; Longstaff \textit{et al}, 1984; Callander and Priestley 1990; Araki, 1991, Alexander and Libretto, 1995).

HFC-134a was not mutagenic to Saccharomyces cerevisiae strain D4 in the presence or absence of the S9 metabolic activation system (Brusick, 1976).

Point mutations in cultured mammalian cells

HFC-134a was not mutagenic to mouse lymphoma L51787 cells with or without metabolic activation (Alexander and Libretto, 1995).

Chromosome aberrations in cultured mammalian cells

An \textit{in vitro} cytogenetic assay was conducted in human lymphocytes with exposure to a range of concentrations of HFC-134a up to 750,000 ppm (3,130,000 mg/m\(^3\)). No statistically or biologically significant increases in chromosomal aberration frequencies were seen at any of the exposure levels tested, in the presence or absence of metabolic activation (Mackay, 1990).

Chinese hamster lung cells were exposed to concentrations of HFC-134a between 400,000 and 1,000,000 ppm (1,670,000 - 4,170,000 mg/m\(^3\)) to investigate clastogenic effects. No induction of chromosomal aberrations was observed with or without metabolic activation (Asakura, 1991).

8.4.2 In vivo

Table 5 summarises results and details of the available \textit{in vivo} studies.

\(^a\) Supernatant of centrifuged 9,000 \(\times\) g liver homogenate, containing the microsome and cytosol fractions, derived from rats previously treated with Aroclor to induce microsomal enzyme activity
### Table 5: The genetic toxicology of HFC-134a in vivo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Species, strain (number and sex/group)</th>
<th>Protocol</th>
<th>Concentration (ppm)</th>
<th>Result</th>
<th>Reference</th>
<th>CoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronucleus frequency</td>
<td>Mouse, NMRI (5 M, 5 F)</td>
<td>Inhalation, 6 h</td>
<td>0, 50,000, 150,000, 500,000 (0, 208,000, 630,000, 2,080,000)</td>
<td>–ve a</td>
<td>Müller and Hofmann, 1989</td>
<td>1a</td>
</tr>
<tr>
<td>Dominant lethal mutations</td>
<td>Mouse, CD1 (15 M, 30 F)</td>
<td>Inhalation 6 h/d, 5 d</td>
<td>0, 1,000, 10,000, 50,000 (0, 4,170, 41,700, 208,000)</td>
<td>–ve</td>
<td>Hodge et al, 1979</td>
<td>1a</td>
</tr>
<tr>
<td>Chromosome aberrations</td>
<td>Rat, Alpk/APfSD Wistar-derived (8 M)</td>
<td>Inhalation, 6 h/d, 5 d</td>
<td>0, 1,000, 10,000, 50,000 (0, 4,170, 208,000)</td>
<td>–ve</td>
<td>Anderson and Richardson, 1979</td>
<td>1a</td>
</tr>
<tr>
<td>Unscheduled DNA synthesis (hepatocytes)</td>
<td>Rat; Alpk/APfSD Wistar-derived (4-5 M)</td>
<td>Inhalation, 6 h</td>
<td>0, 10,000, 50,000, 100,000 (0, 41,700, 208,000, 417,000)</td>
<td>–ve</td>
<td>Trueman, 1990</td>
<td>1a</td>
</tr>
</tbody>
</table>

a –ve, negative
Chromosomal mutation

In a micronucleus assay, NMRI mice were exposed for 6 hours to concentrations of up to 500,000 ppm HFC-134a. The incidence of micronucleated polychromatic erythrocytes in the bone marrow was not statistically significantly different from the controls. The ratio of poly- to normo-chromatic cells remained unaffected by the treatment with HFC-134a (Müller and Hofmann, 1989).

In a dominant lethal assay, CD1 male mice were exposed to up to 50,000 ppm HFC-134a for 5 days. After the last exposure, each male was housed with 2 virgin females for 4 consecutive nights. Further matings with new females were conducted at weekly intervals for a total of 8 times. The study indicated that HFC-134a did not affect male fertility or cause mutagenic effects through sperm (Hodge et al, 1979).

In an in vivo cytogenetic study, groups of 8 male Alpk/APfSD Wistar-derived rats, were exposed to HFC-134a at concentrations of up to 50,000 ppm for 1 or 5 days. After exposure, animals were terminated and slides of bone marrow prepared and examined for chromosomal abnormalities. There were no statistically significant differences between HFC-134a treated groups and the negative control group when total chromosomal aberrations were considered. When abnormalities other than chromosomal gaps were examined, a statistically significant increase was found in the group exposed to 50,000 ppm for a single exposure only. This increase in the mean value was attributable to one animal and the result was not considered as an event of biological significance. The authors concluded that HFC-134a did not induce chromosomal aberrations in the bone marrow cells of rats (Anderson and Richardson, 1979).

Unscheduled DNA synthesis: primary rat hepatocytes

HFC-134a was tested for the ability to induce unscheduled DNA synthesis in an in vivo assay in rat hepatocytes. Male Alpk/APfSD Wistar-derived rats were exposed for 6 hours to HFC-134a concentrations of up to 100,000 ppm. There was no increase in DNA repair activity (Trueman, 1990).

8.4.3 Cell transformation in vitro

HFC-134a was tested for its cell transforming capacity using the Styles cell transformation assay, which makes use of a cell line derived from baby hamster kidney fibroblasts. HFC-134a was shown to be negative (Longstaff et al, 1984; CoR 2e).
8.4.4 Summary

In conclusion, HFC-134a is not mutagenic and does not induce primary DNA damage or cell transformation.

8.5 Chronic toxicity and carcinogenicity

When Han-Ibn Wistar rats were exposed (1 h/d) to concentrations of 0, 2,500, 10,000 or 50,000 ppm HFC-134a (0, 10,400, 41,700, 208,000 mg/m³) for 50 weeks, the animals tolerated the exposures well and no treatment-related effects were observed (Alexander and Libretto, 1995; CoR 1a).

When C57B1 mice were exposed (1 h/d) to concentrations of 0, 10,000, 25,000 or 50,000 ppm HFC-134a (0, 41,700, 104,000, 208,000 mg/m³) for 90 days, the animals tolerated the exposures well and no treatment-related effects were observed (Alexander and Libretto, 1995; CoR 1a).

Beagle dogs (3/sex/group) were exposed (1 h/d) by inhalation to HFC-134a at a concentration of 120,000 ppm (500,000 mg/m³) for 1 year (376 d). Similar groups of dogs were exposed either to air alone or to air containing an additional 12% w/v nitrogen. In addition, groups of dogs (number and sex unspecified) were exposed (2 ×/d) to HFC-134a by instillation into the lung of metered doses of 0.0225, 0.075 or 0.225 g/kg/d by oropharyngeal tube. Exposure to HFC-134a was well tolerated by the dogs in both studies. No treatment-related effects were reported in either study (Alexander and Libretto, 1995; Alexander et al., 1995a; CoR 1a).

Alpk/APfSD Wistar-derived rats (36/sex/group) received (5 d/wk) by gavage 300 mg/kgbw HFC-134a dissolved in corn oil for 52 weeks and were then maintained for life. Two similar sized control groups were dosed with corn oil only and one control group received no treatment. The study was terminated after 125 weeks. HFC-134a did not increase the incidence of tumours in any of the organs from the treated group when compared with the control groups (Longstaff et al., 1984; CoR 2e).

In a combined chronic toxicity-carcinogenicity study, Alpk/APfSD Wistar-derived rats (85/sex/group) were exposed (6 h/d, 5 d/wk) by whole-body inhalation to 0, 2,500, 10,000 or 50,000 ppm HFC-134a (0, 10,400, 41,700, 208,000 mg/m³) for 52 weeks, when 10 rats of either sex from each group were killed; the remaining rats were continued to be exposed until terminal kill after 104 weeks. The highest concentration was chosen as the limit dose (5% in air, i.e. 50,000 ppm). All groups had a similar survival rate. The observed differences in body weight and food consumption reflected only biological variation and were not compound-related. There were no treatment-related changes in clinical chemistry or haematology parameters in any of the exposed animals. Small increases in urinary fluoride levels were seen on occasion in groups
exposed to 10,000 and 50,000 ppm, but were considered to be of no biological significance. The only treatment-related effect of toxicological significance was confined to the testes of male rats exposed to 50,000 ppm. There was a statistically significant increase in the weight of the testes of treated animals versus controls and there was an increased incidence of Leydig cell hyperplasia and benign Leydig cell tumours (see Table 6). The NOEL was considered to be 10,000 ppm HFC-134a (Hext and Parr-Dobrzanski, 1993; CoR 1a).

**Table 6: Number of animals (n = 85) with Leydig cell tumours**
(Hext and Parr-Dobrzanski, 1993)

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>27</td>
</tr>
<tr>
<td>Adenoma</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes all animals from interim, intercurrent and terminal killings
<sup>b</sup> Data from 79 animals
<sup>c</sup> Significantly different from control values p < 0.01 (Fisher's exact test)

Han-Ibn Wistar rats (60/sex/group) and B6C3F1 mice (60/sex/group) were exposed (1 h/d; snout-only) to concentrations of 0, 2,500, 10,000 or 50,000 ppm HFC-134a (0, 10,400, 41,700, 208,000 mg/m³) for their life-time (rats 108 weeks, mice 106 weeks). No treatment-related effects, either neoplastic or non-neoplastic were observed (Alexander and Libretto, 1995; Alexander et al, 1995b; CoR 1a).

**8.5.1 Mechanistic studies**

Various studies have been conducted *in vivo* and *in vitro* to investigate the potential mechanism of formation of testicular Leydig cell tumours in male rats exposed to HFC-134a.

**In vivo**

Sprague-Dawley rats (5/sex/group) were exposed (1 h/d, whole-body) by inhalation to 100,000 ppm HFC-134a (417,000 mg/m³) for 14 days. The pituitary gonadotropin and prolactin secretion was monitored on days 1 and 14 by performing a luteinising hormone-releasing hormone (LHRH) test (10 µg/kg bw subcutaneous, luteinising/follicle stimulating hormone [LH/FSH] response 1 hour after test injection). At the end of the exposure period, 24 hours after the last inhalation, animals were killed and the pituitary glands removed for hormone assay.
Marked changes were found in the hormone content of the pituitary gland, both in female and male rats. The pituitary content of LH and FSH was significantly reduced, whilst the pituitary prolactin content was significantly increased. On the last day (14), the serum concentrations of LH showed no changes as judged by the response of LH in the LHRH stimulation test, but there was an increase in pituitary FSH responsiveness. The response of FSH to the LHRH test dose was nearly 4-fold in treated male rats, and doubled in treated females. There was no change in serum prolactin after test injection of thyrotropin releasing hormone (TRH) on day 10 of the study (Sandow et al, 1994).

To investigate the effects of HFC-134a on pituitary-gonadal function, Sprague-Dawley rats (10/sex/group) were exposed (6 h/d) to 0 or 50,000 ppm HFC-134a (0, 208,000 mg/m³) for 14 days; the exposure duration on the last day was limited to 2.5 hours. Following the exposure on day 10, pituitary prolactin secretion was stimulated by intraperitoneal injection of mono-iodo-tyrosine (1 mg/rat). After 20 minutes, blood samples were taken and analysed for prolactin using a specific radio-immunoassay (RIA) method. On the last day (14), after 1 h exposure, a blood sample was taken from each rat and analysed for basal LH and FSH levels using specific RIA methods. At that time, a dynamic function test for pituitary LH/FSH secretion was also performed by the subcutaneous administration of buserelin (20 ng/rat). After a further 1.5-hour exposure, the blood was analysed for LH and FSH. In male rats, serum testosterone levels were determined on day 1 (after 6 h exposure) and on day 14 (both before and after the injection of buserelin) using a specific RIA method. All rats were sacrificed on day 14 following the second period of exposure, after which the pituitary glands were removed and prepared for the determination of LHRH receptors (125-I-buserelin used as ligand) and their content of LH, FSH and prolactin. In addition, ovaries and testes were removed and analysed for ovarian oestradiol and progesterone content and testicular testosterone content using specific RIA methods.

On day 10, the prolactin response in male rats exposed to HFC-134a was reduced by 30%, when compared to controls. Exposure to HFC-134a had no statistically significant effect on the stimulation of serum LH or FSH levels on day 14, nor did it have any effect on pituitary LH, FSH or prolactin content. Exposure to HFC-134a resulted, on day 14, in a reduction in testicular testosterone levels by almost 50%, a slight increase in basal serum testosterone levels and a marked impairment of the testosterone response to buserelin. In female rats, exposure to HFC-34a had no effect on the stimulation of LH and FSH secretion following the administration of buserelin (day 14). The levels of pituitary FSH had declined and those of prolactin were slightly reduced. Serum prolactin levels (both basal and moniodotyrosine-stimulated) were unaffected, as were ovarian oestradiol and progesterone content (Sandow et al, 1996).
In vitro

The effects of HFC-134a and its metabolites TFA, TFAA and TFEth (Section 7.1) on testicular cell function have also been studied in cultured Leydig cells and Sertoli cells, and in Sertoli-germ cell co-cultures derived from Sprague-Dawley rats. Vapour concentrations of 750,000 ppm HFC-134a (3,130,000 mg/m³), either exposed directly or by 24-hour pre-treatment, were found to be non-cytotoxic to Leydig cells, Sertoli cells and Sertoli-germ cells. In addition, HFC-134a had no biologically significant effects on basal or hormone stimulated testosterone production in Leydig cells, no effects on the morphology or on basal or dibutyryl cyclic adenosine monophosphate (dbcAMP)-stimulated lactate and pyruvate production in Sertoli cells. Neither were there any effects on the morphology, cell loss, lactate dehydrogenase-X*a (LDHX) leakage and lactate and pyruvate production of Sertoli cells or on testosterone production in Sertoli-germ cell cultures.

TFAA was not cytotoxic to Leydig cells at a concentration of 50 mmol/l. At concentrations above 5 mmol/l, TFAA caused a dose-dependent reduction in basal testosterone production and, at concentrations > 0.5 mmol/l, caused a dose-dependent reduction in hormonally-stimulated testosterone production in Leydig cells. TFAA was found to be cytotoxic to Sertoli cells at concentrations > 0.75 mmol/l. Exposure of Sertoli cells to 0.75 mmol TFAA/l for 24 hours led to marked vacuolation and condensed, darkly staining nuclei. Concentrations of TFA > 0.05 or 0.1 mmol/l caused dose-dependent decreases in basal and dbcAMP-stimulated lactate and pyruvate production in Sertoli cells. TFAA was also found to be cytotoxic to Sertoli-germ cells at concentrations > 0.75 mmol/l. Exposure of Sertoli-germ cells to 0.75 mmol TFAA/l for 24 hours resulted in the loss of most germ cells and to marked vacuolation of the Sertoli cells. Concentrations of TFAA > 0.01 mmol/l caused a dose-dependent increase in LDHX leakage from Sertoli-germ cells. A concentration of 0.75 mmol/l TFAA caused marginal decreases in basal and dbcAMP-stimulated lactate production by Sertoli-germ cell cultures but had no significant effect on pyruvate levels.

Trifluoroacetic acid (TFA) was cytotoxic to Leydig cells at concentrations above 20 mmol/l. At concentrations > 5 mmol/l, TFAA, at non-cytotoxic concentrations, had no effect on basal testosterone production and equivocal effects on hormonally-stimulated testosterone production in Leydig cells. TFA was found to be cytotoxic to Sertoli cells at concentrations > 15 mmol/l. Exposure of Sertoli cells to 15 mmol TFA/l for 24 hours had no effect on their morphology. Concentrations > 15 mmol TFA/l had no significant effects on basal lactate and both basal and dbcAMP-stimulated pyruvate production in Sertoli cells but did cause a dose-dependent enhancement of dbcAMP-stimulated lactate production. TFA was also found to be cytotoxic to Sertoli-germ cells at concentrations > 15 mmol/l. Exposure of Sertoli-germ cells to concentrations of TFA up to 15 mmol/l for 24 hours had no effect on their morphology, had no

*a A testis-specific LDH isoenzyme located in pachytene spermatocytes
effect on LDHX leakage and no significant effects on basal and dbcAMP-stimulated lactate and pyruvate production.

TFEth was found not to be cytotoxic to Leydig cells at concentrations up to 100 mmol/l. At a concentration of 50 mmol/l, TFEth had no effect on basal testosterone production and equivocal effects on hormonally-stimulated testosterone production in Leydig cell cultures. TFEth was found to be cytotoxic to Sertoli cells at concentrations > 20 mmol/l. Exposure of Sertoli cells to 20 mmol/l TFEth for 24 hours had no significant effects on both basal and dbcAMP-stimulated lactate or pyruvate production. TFEth was found not to be cytotoxic to Sertoli-germ cells at concentrations up to 50 mmol/l. Exposure of Sertoli-germ cells to 20 mmol TFEth/l for 24 hours had no effect on their morphology or cell loss, no effect on LDHX leakage and no significant effects on basal and dbcAMP-stimulated lactate and pyruvate production (Williams, 1997).

**Evaluation**

Whilst HFC-134a did not have any significant effects in this study, its metabolite, TFA, did show effects, particularly in the Sertoli-germ cells. The effects seen are indicative of altered cell function and provide limited support for the hypothesis that the induction of Leydig cell tumours by HFC-134a may have arisen because of its metabolism to TFAA, resulting in biochemical perturbations of the function of Leydig and/or Sertoli cells. The absence of significant effects of TFE in these *in vitro* test systems probably reflects an inadequacy in the model, because it is known that TFE is a testicular toxicant, most probably due to its metabolism to TFAA (Lloyd *et al.*, 1988).

**Discussion**

Benign tumours of the testicular interstitial cells (Leydig cell adenoma) are common in the ageing rat. The spontaneous incidence of this tumour type is variable from one strain to another, ranging from a few percent in Sprague-Dawley rats up to 100% in some Wistar-derived and Fisher 344 rats (Bär, 1992). These tumours do not usually progress to malignancy in the rat (e.g. no malignant Leydig cells tumours found in several thousands of control Fisher rats) (Boorman *et al.*, 1990; Iawata *et al.*, 1991). An increased incidence of Leydig cell tumours has been described following exposure to a large number of substances covering a wide variety of chemical structures e.g. isradipine (Roberts *et al.*, 1989), mesulergine (Prentice *et al.*, 1992), cimetidine (Leslie *et al.*, 1981), hydralazine, carbamazepine (Griffith, 1988) and even such a common dietary component as lactose (Bär, 1992). Leydig cell tumours are known to secrete sex hormones (e.g. testosterone, dihydroandrosterone, oestradiol) and it is thought that the high incidence of hyperplasia and tumours of the Leydig cell in aging rats is related to senile endocrine disturbance (Mostofi and Price, 1973).
HFC-134a induced Leydig cell hyperplasia and tumours in the rat occurred late in life and were not associated with increased mortality. HFC-134a, like many other known Leydig cell carcinogens, is not mutagenic (Section 8.4). Consequently, the increased incidence of Leydig cell tumours observed in rats exposed to HFC-134a is attributable to a non-genotoxic mechanism. Non-genotoxic mechanisms have been frequently associated with hormonal imbalances, especially an imbalance of sex hormones (Neumann, 1991). The observation that exposure to HFC-134a can reduce the stimulatory effects of moniodotyrosine on prolactin secretion and cause a marked reduction in testicular testosterone levels suggests that a hormonal mechanism might be responsible for the increase incidence of Leydig cell tumours, possibly by increased feedback of Leydig cell production and secretion of testosterone in response to the decreased tissue levels of the hormone. In addition, HFC-134a has a significant effect on pituitary gonadotropin secretion (augmented FSH release) and hormone content (decreased LH/FSH content and augmented prolactin content in the rat). The changes are of sufficient magnitude to explain changes in Leydig cell function which could ultimately, after long term exposure, result in Leydig cell hyperplasia. Such endocrine changes are of a reversible nature in rats if the period of exposure is limited. In long term toxicology studies, the present findings would be compatible with the late onset of Leydig cell hyperplasia as a reaction to functional changes in the secretion of LH, FSH and prolactin in the rat.

The consequences of this finding for humans are considered to be biologically and toxicologically irrelevant. The incidence of Leydig cell tumours in humans is extremely low, in contrast to the rat, representing less than 3% of all testicular neoplasms (Mostofi and Price, 1973). The rarity of Leydig cell tumours in man, compared to the high spontaneous incidence in the rat, demonstrate that these tumours are not relevant to humans. Consequently the increased frequency of the benign Leydig cell tumours observed in rats exposed to HFC-134a at the high concentration of 50,000 ppm (208,000 mg/m³) is considered not to indicate a tumorigenic risk to humans.

8.6 Reproductive effects, embryotoxicity and teratology

8.6.1 Fertility

No significant effects on reproductive performance were seen in a dominant lethal study in mice exposed to HFC-134a (Hodge et al., 1979; CoR 1a) (Section 8.4.2).

In a multi-generation reproductive toxicity study, AHA rats (F₀ generation) (30/sex/group) were exposed (1 h/d, snout-only) to HFC-134a at concentrations of 0, 2,500, 10,000 and 50,000 ppm (0, 10,400, 41,700, 208,000 mg/m³) throughout gametogenesis (10 weeks before pairing for males; 3 weeks before pairing for females) and during mating. The F₀ males were further exposed until the week 18 of exposure, and then killed. Fourteen of the pregnant F₀ females from each group were further exposed until day 19 post coitum and terminated on day 20 post coitum for
examination of their uterine contents and ovaries. The remaining F₀ females were further exposed until day 20 post coitum, at which time exposures were suspended to allow parturition to occur. Exposure of these F₀ females recommenced at the same concentrations on day 1 post partum until day 21 post partum, at which time the dams were terminated and the male and female F₁ pups were separated. One male and one female F₁ pup was retained from each litter (12 litters/group) and raised to maturity. The remaining F₁ pups were killed.

The selected F₁ rats were mated when they were approximately 70 days old. The survival and development of the resulting F₂ progeny was monitored for 21 days post partum. F₁ males failing to mate were examined post mortem. One male and one female F₂ pup were retained from each of the 8 litters/group and raised to maturity. The remaining F₂ pups and the F₁ females were killed at this time. Once the selected F₂ progeny had reached sexual maturity, they too were killed. The effect of exposure to HFC-134a on fertility and development was assessed in terms of clinical observation, body weights, breeding performance of the F₀ and F₁ generations, analysis of parturition statistics and the development of the F₁ and F₂ generations. No treatment-related effects on reproductive performance, maturation or development of the offspring were reported (Alexander et al., 1996; CoR 1a).

8.6.2 Embryotoxicity and teratology

Pregnant Alpk/APfSD Wistar-derived rats (29 - 30/group) were exposed (6 h/d) to 0, 1,000, 10,000 or 50,000 ppm (0, 4,170, 41,700, 208,000 mg/m³) HFC-134a from day 6 to 15 of gestation. The exposure to HFC-134a produced abnormal clinical signs but did not affect the maternal body weights. Mean foetal weights were slightly but significantly lower in the offspring of rats exposed to 50,000 ppm. Embryonic and foetal survival were unaffected by the treatment. There was no evidence for teratogenicity but skeletal ossification was slightly retarded in the top dose (50,000 ppm). It was concluded that HFC-134a was neither teratogenic nor embryotoxic at levels up to 50,000 ppm, but at this highest level HFC-134a might be slightly foetotoxic (Hodge et al., 1980; CoR 1a).

In a study using similar exposure conditions to the above, pregnant Sprague-Dawley rats (7/group) were exposed to concentrations of 0, 30,000, 100,000 or 300,000 ppm (0, 125,000, 417,000, 1,250,000 mg/m³) HFC-134a. No teratogenic effects were observed although there was some decrease of maternal body weight gain and retarded foetal development in the form of delayed ossification. The minimum maternal effect exposure level was demonstrated to be 100,000 ppm, and the minimum embryo/foetal effect exposure level was demonstrated to be 300,000 ppm (Lu, 1981; CoR 1a).
Female New Zealand White rabbits (28/group) were exposed (6 h/d) by inhalation to 0, 2,500, 10,000 and 40,000 ppm (0, 10,420, 41,700, 167,000 mg/m \(^3\)) HFC-134a from days 7 to 19 of gestation. Exposure to concentrations of 10,000 and 40,000 ppm HFC-134a was associated with slight maternal toxicity manifest as reduced body weight gain and food consumption. There was no evidence for maternal toxicity at the exposure level of 2,500 ppm. There was no evidence of embryotoxicity or foetotoxicity at any exposure level (Collins et al, 1995; CoR 1a).

Pregnant female AHA rats (F\(_0\) generation) (41/group) were exposed to HFC-134a at concentrations of 0, 2,500, 10,000 and 50,000 ppm (0, 10,400, 41,700, 208,000 mg/m \(^3\)) from day 17 to 20 of gestation. Exposure recommenced at the same concentrations on day 1 post partum and continued until day 21 post partum. The females were allowed to litter and rear their young (F\(_1\) generation). On day 21, one male and one female F\(_1\) pup were retained from each of the 20 litters/group and raised to maturity. The remaining F\(_1\) pups and their mothers were terminated at this time. The selected F\(_1\) rats were mated when they were approximately 84 days old and, on day 20 of pregnancy, the females were terminated to allow the examination of their uterine contents and ovaries. The F\(_1\) males were also terminated at this time.

The effect of exposure to HFC-134a on fertility and development was assessed in terms of clinical observation, body weights, breeding performance of the F\(_0\) and F\(_1\) generations and the analysis of parturition statistics. The physical development of the F\(_1\) generation was assessed by measuring the time of appearance of key developmental markers. Functional development was assessed after 4 weeks, when locomotor co-ordination was measured using an accelerating rotarod, after 5 weeks by assessing spontaneous exploratory performance in an unfamiliar surrounding and after 7 to 9 weeks, when learning, memory and reverse learning were assessed using the Biel maze. No treatment-related effects on reproductive performance, maturation or development of the offspring were reported.

Structural development was also assessed by examining foetuses from the F\(_0\) generation of the previously described multi-generation reproductive toxicity study (Section 8.6.1). No treatment-related effects upon the incidence, type or distribution of visceral or skeletal abnormalities were reported (Alexander et al, 1996; CoR 1a).

**8.7 Neurological studies**

Alpk/AskSD Wistar-derived rats (5/sex/group) were exposed to HFC-134a at target concentrations of 0, 150,000 or 200,000 ppm (0, 625,000, 834,000 mg/m \(^3\)) for 1 to 2 hours. Further groups of 5 male or female rats were pre-treated with ethanol and subsequently exposed to 0 or 150,000 ppm (1.0 g ethanol/kgbw) or 200,000 ppm (5.0 g ethanol/kgbw) HFC-34a for 1 to 2 hours. A neurological examination was conducted on each rat before treatment and a
quantitative assessment of sensory perception (tail flick test) was performed on each animal approximately 1 hour after the initiation of exposure. No evidence of neurological dysfunction was observed in any of the treated groups, with or without pre-treatment with ethanol. Female rats exposed to 200,000 ppm HFC-134a showed a small but statistically significant increase in tail flick time. This effect was not seen in male rats exposed to HFC-134a, with or without ethanol pre-treatment, nor in pre-treated female rats. The study showed that there were no significant additive or synergistic effects between ethanol and HFC-134a on the neurological system in the rat (Pinto, 1998; CoR 1a).

Male Wistar rats (10/group) were exposed to HFC-134a or dichlorodifluoromethane (CFC-12) while performing in a rotarod/motorised running wheel apparatus to steadily increasing concentrations of HFC-134a or CFC-12 for up to 30 minutes, to a maximum concentration of 470,000 ppm (1,960,000 mg/m³), with or without replacement oxygen. The times to loss of equilibrium, loss of hind limb function, loss of forelimb function and loss of righting reflex were measured. In rats exposed to HFC-134a, loss of equilibrium occurred after about 200 seconds, at which time the test atmosphere concentration had reached approximately 200,000 ppm. Loss of righting reflex occurred after about 800 seconds at 380,000 ppm. The replacement of oxygen had marginal effects on the times to effect, although it appeared to protect against convulsions that were seen in some rats exposed to either HFC-134a or CFC 12 without oxygen replacement. In a separate experiment, rats showed a rapid (< 60 s) recovery from these acute effects on the central nervous system and no evidence of long-term neurological deficits was seen 30 days following exposure (Ritchie et al, 2001; CoR 1a).

In an operant behaviour study, male Wistar rats (4/group) were exposed (15 min/d) to HFC-134a or CFC-12 concentrations increasing from 40,000 to 140,000 ppm (167,000 - 584,000 mg/m³) for 20 successive days. Behaviour was assessed by the number of food rewards earned by the subject during exposure following a standard schedule of training. The number of food rewards earned by rats exposed to 140,000 ppm HFC-134a was significantly reduced when compared to controls. NO significant reduction occurred at lower concentrations. For the neurobehavioural endpoints examined, HFC-134a was shown to induce deficits at somewhat lower concentrations when compared to CFC-12 exposure (Ritchie et al, 2001; CoR 1a).
9. EFFECTS ON HUMANS

No adverse health effects in humans from exposure to HFC-134a have been reported.

HFC-134a is a replacement for various CFCs in refrigeration and aerosol applications, including as a propellant in metered dose inhalers for medical aerosols. In clinical trials, it has been shown to be an effective and safe propellant (Alexander, 1995; Harrison et al, 1996; Blumenthal et al, 1997; Hermann et al, 1998; all CoR 2a). These evaluations used replicate doses from metered dose inhalers and the exposure concentrations were probably below levels that might be encountered in the workplace.

Therefore, a clinical study using larger doses was conducted in which HFC-134a vapour was administered (1 h/wk, whole-body exposure) for 8 weeks to healthy volunteers (4 male, 4 female) by inhalation first to air alone and then during the succeeding weeks to ascending concentrations of 1,000, 2,000, 4,000 and 8,000 ppm (4,170, 8,340, 16,700, 33,400 mg/m³) interspersed with a second air exposure and two exposures to CFC-12 at 1,000 and 4,000 ppm. Blood pressure, blood levels of HFC-134a, pulse, cardiac function, respiratory function and effects on the central nervous system were measured and evaluated. There were no observed adverse effects, no evidence of effects on the central nervous system, and no symptoms of upper respiratory tract irritation. HFC-134a blood concentrations increased rapidly and in an exposure-dependent manner. They approached steady state within 30 minutes and tended to be higher in males than females. Following the end of the exposure period, blood concentrations declined rapidly, predominantly biphasically and independent of exposure concentration. The alpha elimination half-life ($t_{1/2\alpha}$) was less than 11 minutes, while $t_{1/2\beta}$ was 42 minutes. The mean residence time was 44 minutes. It was concluded that, under these test conditions, human exposure to HFC-134a did not result in any adverse effects on pulse, blood pressure, electrocardiogram or lung function (Emmen et al, 2000; CoR 1a).
## LIST OF SPECIAL ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL</td>
<td>Acute Exposure Guideline Level</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstracts Service</td>
</tr>
<tr>
<td>CFC</td>
<td>Chlorofluorocarbon</td>
</tr>
<tr>
<td>CoR</td>
<td>Code of reliability</td>
</tr>
<tr>
<td>dbcAMP</td>
<td>Dibutyl cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Median effective concentration</td>
</tr>
<tr>
<td>EINECS</td>
<td>European inventory of existing commercial chemical substances</td>
</tr>
<tr>
<td>EQC</td>
<td>Equilibrium criterion</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>GWP</td>
<td>Global warming potential</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HCFC</td>
<td>Hydrochlorofluorocarbon</td>
</tr>
<tr>
<td>HFC</td>
<td>Hydrofluorocarbon</td>
</tr>
<tr>
<td>hPa</td>
<td>Hectopascal</td>
</tr>
<tr>
<td>ITH</td>
<td>Integration time horizon</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>JACC</td>
<td>Joint Assessment of Commodity Chemicals</td>
</tr>
<tr>
<td>kgbw</td>
<td>Kilogramme body weight</td>
</tr>
<tr>
<td>kt</td>
<td>Kilotonne</td>
</tr>
<tr>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Median lethal concentration</td>
</tr>
<tr>
<td>LDHX</td>
<td>Lactate dehydrogenase-X</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinising hormone</td>
</tr>
<tr>
<td>LHRH</td>
<td>Luteinising hormone-releasing hormone</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>µg</td>
<td>Microgramme</td>
</tr>
<tr>
<td>µl</td>
<td>Microlitre</td>
</tr>
<tr>
<td>mol</td>
<td>Mole</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogramme</td>
</tr>
<tr>
<td>Mt</td>
<td>Megatonne</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOEC</td>
<td>No-observed-effect concentration</td>
</tr>
<tr>
<td>NOEL</td>
<td>No-observed-effect level</td>
</tr>
<tr>
<td>ODP</td>
<td>Ozone depleting potential</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>Pa</td>
<td>Pascal</td>
</tr>
<tr>
<td>Acronym</td>
<td>Abbreviation</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>PAFT</td>
<td>Programme for Alternative Fluorocarbon Toxicity Testing</td>
</tr>
<tr>
<td>ppb</td>
<td>Parts per billion (volume)</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million (volume)</td>
</tr>
<tr>
<td>ppt</td>
<td>Parts per trillion (volume)</td>
</tr>
<tr>
<td>s</td>
<td>Second</td>
</tr>
<tr>
<td>STEL</td>
<td>Short-term exposure limit</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetaldehyde</td>
</tr>
<tr>
<td>TFEth</td>
<td>Trifluoroethanol</td>
</tr>
<tr>
<td>TWA</td>
<td>Time-weighted average</td>
</tr>
<tr>
<td>W</td>
<td>Watt</td>
</tr>
</tbody>
</table>

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### APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES
Adapted from Klimisch *et al* (1997)

<table>
<thead>
<tr>
<th>Code of Reliability (CoR)</th>
<th>Category of reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reliable without restriction</td>
</tr>
<tr>
<td>1a</td>
<td>GLP guideline study (OECD, EC, EPA, FDA, <em>etc.</em>)</td>
</tr>
<tr>
<td>1b</td>
<td>Comparable to guideline study</td>
</tr>
<tr>
<td>1c</td>
<td>Test procedure in accordance with national standard methods (AFNOR, DIN, <em>etc.</em>)</td>
</tr>
<tr>
<td>1d</td>
<td>Test procedure in accordance with generally accepted scientific standards and described in sufficient detail</td>
</tr>
<tr>
<td>2</td>
<td>Reliable with restrictions</td>
</tr>
<tr>
<td>2a</td>
<td>Guideline study without detailed documentation</td>
</tr>
<tr>
<td>2b</td>
<td>Guideline study with acceptable restrictions</td>
</tr>
<tr>
<td>2c</td>
<td>Comparable to guideline study with acceptable restrictions</td>
</tr>
<tr>
<td>2d</td>
<td>Test procedure in accordance with national standard methods with acceptable restrictions</td>
</tr>
<tr>
<td>2e</td>
<td>Study well documented, meets generally accepted scientific principles, acceptable for assessment</td>
</tr>
<tr>
<td>2f</td>
<td>Accepted calculation method</td>
</tr>
<tr>
<td>2g</td>
<td>Data from handbook or collection of data</td>
</tr>
<tr>
<td>3</td>
<td>Not reliable</td>
</tr>
<tr>
<td>3a</td>
<td>Documentation insufficient for assessment</td>
</tr>
<tr>
<td>3b</td>
<td>Significant methodological deficiencies</td>
</tr>
<tr>
<td>3c</td>
<td>Unsuitable test system</td>
</tr>
<tr>
<td>4</td>
<td>Not assignable</td>
</tr>
<tr>
<td>4a</td>
<td>Abstract</td>
</tr>
<tr>
<td>4b</td>
<td>Secondary literature</td>
</tr>
<tr>
<td>4c</td>
<td>Original reference not yet available</td>
</tr>
<tr>
<td>4d</td>
<td>Original reference not translated</td>
</tr>
<tr>
<td>4e</td>
<td>Documentation insufficient for assessment</td>
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</table>
APPENDIX B: NAMING AND NUMBERING SYSTEM FOR FLUOROCARBON COMPOUNDS

The naming and numbering system currently used by industry was officially adopted as Standard 34 of the American Society of Heating, Refrigeration, and Air-conditioning Engineers (ASHRAE) on June 3, 1957 (Du Pont, 1999).

B.1 Prefixes

These prefixes are generally applicable:

- FC = Fluorocarbon
- CFC = Chlorofluorocarbon
- HFC = Hydrofluorocarbon
- PFC = Perfluorocarbon (also Perfluorocompound, Persistent Fluorinated Compound)
- HFOC = Hydrofluoroether
- HCFC = Hydrochlorofluorocarbon
- FOC = Fluoroether

B.2 Numbering code

The first digit from the right is the number of fluorine atoms in the molecule. The second digit from the right is one more than the number of hydrogen atoms in the molecule. The third digit from the right is one less than the number of carbon atoms in the molecule (omit if zero).

The number of chlorine atoms in the compound is calculated by subtracting the sum of fluorine and hydrogen atoms from the total atoms which can be connected to the carbon atoms. If some of the chlorine has been replaced by bromine, then the number is followed by a "B" and the number of chlorine atoms so replaced.

The fourth digit from the right indicates the number of double bonds in the molecule, for example:

- PFC-116 = 6 Fs, 0 Hs, 2 Cs and 0 Cls → C₂F₆
- HFC-23 = 3 Fs, 1 H, 1 C, and 0 Cls → CF₃H
- PFC-1216 = 6 Fs, 0 Hs, 3 Cs, 0 Cls with 1 double bond → C₃F₆ → CF₂=CF-CF₃

For cyclic molecules, the letter C is used before the identifying number, for example:
• PFC-C318 = 8 Fs, 0 Hs, 4 Cs and 0 Cls with cyclic structure → c-C₄F₈

For isomeric compounds, each has the same number designation, but the various isomers are indicated by a lowercase letter following the number; the letters are assigned based on the symmetry of the molecule. The most symmetrical structure has no letter, followed by the next most symmetrical isomer designated "a", and so on. The symmetry is determined by summing the atomic weights of all atoms attached to each carbon, and comparing the two numbers. The smaller their difference, the more symmetrical the molecule. For example C₂H₂F₄ can have two structural isomers:

• CF₂H-CF₂H, more symmetrical, HFC-134
• CF₃-CFH₂, less symmetrical, HFC-134a

B.3 Extension to 3-carbon molecules

For C3s, the isomer designation is slightly different, and uses a two-letter code. The codes below are used to determine the substituents on the central carbon, which determines the first letter of the code. The second letter in the code designates the various isomers based on symmetry, with the most symmetrical structure designated "a", and so forth.

B.4 Letter central carbon

• a = CCl₂
• b = CCIF
• c = CF₂
• d = CClH
• e = CHF
• f = CH₂

For example:

HFC-236fa = C₃F₆H₂ → Central carbon designated "f" → CH₂ → "a" designation → CF₂CH₂CF₃

B.5 C4 and larger molecules

For 4-carbon atom and larger molecules, string together the letter designations from the above and following lists to indicate the current isomer. Always start either at the molecule’s more
fluorinated end or at the end needing the least number of suffix letters to assign the structure. If a digit is larger than 9, it is offset by a dash.

- $j = \text{CCl}_3$
- $k = \text{CCl}_2\text{F}$
- $l = \text{CCIF}_2$
- $m = \text{CF}_3$
- $n = \text{CHCl}_2$
- $o = \text{CH}_2\text{Cl}$
- $p = \text{CHF}_2$
- $q = \text{CH}_2\text{F}$
- $r = \text{CHClIF}$
- $s = \text{CH}_3$
- $t = \text{C}$
- $x = \text{CCl}$
- $y = \text{CF}$
- $z = \text{CH}$

Example: HFC-43-10mee = 10 Fs, 2 Hs, 5 Cs, no Cls $\rightarrow \text{C}_5\text{H}_2\text{F}_{10}$

- $m$ indicates $\text{CF}_3 \ldots \text{CF}_3$
- $e$ indicates CHF, so $\text{CF}_3\text{CHF}$
- $e$ indicates CHF, so $\text{CF}_3\text{CHFCHF}$
- HFC-43-10mee $\rightarrow \text{CF}_3\text{CHFCHFCHFCF}_2\text{CF}_3$

The assignment of a string of letters, to denote structural groups, is stopped when the structure is unambiguous (i.e. one does not need to call the compound HFC-43-10mee cm, since once one reaches "mee", one knows that 5 fluorine atoms still need to be attached to the remaining two carbons, so the rest of the molecule must be $-\text{CF}_2\text{CF}_3$).
APPENDIX C: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR

Conversion factors for vapour concentrations in air can be calculated from the molar volume of an ideal gas at 0°C: 22.4136 litre.

\[
1 \text{ mg/m}^3 = \frac{22.4136}{\text{Mw}} \times \frac{1,013.25}{P} \times \frac{(273+T)}{273} \text{ ppm} \quad \text{(Eq. B.1)}
\]

\[
1 \text{ ppm} = \frac{\text{Mw}}{22.4136} \times \frac{P}{1,013.25} \times \frac{273}{(273+T)} \text{ mg/m}^3 \quad \text{(Eq. B.2)}
\]

where Mw = molecular weight, T = temperature (°C) and P = pressure

For European standard conditions, 20°C and 1,013.25 hPa (=1 atm = 760 mm Hg), the formulae become:

\[
1 \text{ mg/m}^3 = \frac{24.0556}{\text{Mw}} \text{ ppm} \quad \text{(Eq. B.3)}
\]

\[
1 \text{ ppm} = \frac{\text{Mw}}{24.0556} \text{ mg/m}^3 \quad \text{(Eq. B.4)}
\]

In the USA and other countries 25°C is used, and the formulae are:

\[
1 \text{ mg/m}^3 = \frac{24.4661}{\text{Mw}} \text{ ppm} \quad \text{(Eq. B.5)}
\]

\[
1 \text{ ppm} = \frac{\text{Mw}}{24.4661} \text{ mg/m}^3 \quad \text{(Eq. B.6)}
\]
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<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>Good Laboratory Practice (Published October 1979)</td>
</tr>
<tr>
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</tr>
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<tr>
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</tr>
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</tr>
<tr>
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<td>Immunotoxicity: Hazard Identification and Risk Characterisation (Published September 1994)</td>
</tr>
<tr>
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</tr>
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</tr>
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</tr>
<tr>
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<td>Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment (Published September 2000)</td>
</tr>
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</tr>
<tr>
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</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Publication Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Melamine</td>
<td>February 1983</td>
</tr>
<tr>
<td>2</td>
<td>1,4-Dioxane</td>
<td>February 1983</td>
</tr>
<tr>
<td>3</td>
<td>Methyl Ethyl Ketone</td>
<td>February 1983</td>
</tr>
<tr>
<td>4</td>
<td>Methylene Chloride</td>
<td>January 1984</td>
</tr>
<tr>
<td>5</td>
<td>Vinilidene Chloride</td>
<td>August 1985</td>
</tr>
<tr>
<td>6</td>
<td>Xylenes</td>
<td>June 1986</td>
</tr>
<tr>
<td>7</td>
<td>Ethylbenzene</td>
<td>August 1986</td>
</tr>
<tr>
<td>8</td>
<td>Methyl Isobutyl Ketone</td>
<td>May 1987</td>
</tr>
<tr>
<td>9</td>
<td>Chlorodifluoromethane</td>
<td>October 1989</td>
</tr>
<tr>
<td>10</td>
<td>Isophorone</td>
<td>September 1989</td>
</tr>
<tr>
<td>11</td>
<td>1,2-Dichloro-1,1-difluoroethane (HFA-132b)</td>
<td>May 1990</td>
</tr>
<tr>
<td>12</td>
<td>1-Chloro-1,2,2,2-tetrafluoroethane (HFA-124)</td>
<td>May 1990</td>
</tr>
<tr>
<td>13</td>
<td>1,1-Dichloro-2,2,2-trifluoroethane (HFA-123)</td>
<td>May 1990</td>
</tr>
<tr>
<td>14</td>
<td>1-Chloro-2,2,2-trifluoromethane (HFA-133a)</td>
<td>August 1990</td>
</tr>
<tr>
<td>15</td>
<td>1-Fluoro 1,1-dichloroethane (HFA-141B)</td>
<td>August 1990</td>
</tr>
<tr>
<td>16</td>
<td>Dichlorofluoromethane</td>
<td>August 1990</td>
</tr>
<tr>
<td>17</td>
<td>1-Chloro-1,1-difluoroethane (HFA-142b)</td>
<td>August 1990</td>
</tr>
<tr>
<td>18</td>
<td>Vinyl Acetate</td>
<td>February 1991</td>
</tr>
<tr>
<td>19</td>
<td>Dicyclopentadiene</td>
<td>July 1991</td>
</tr>
<tr>
<td>20</td>
<td>Tris-/Bis-Mono-(2 ethylhexyl) phosphate</td>
<td>May 1992</td>
</tr>
<tr>
<td>21</td>
<td>Tris-(2-butoxyethyl)-phosphate (CAS:78-51-3)</td>
<td>March 1992</td>
</tr>
<tr>
<td>22</td>
<td>Hydrogen Peroxide</td>
<td>January 1993</td>
</tr>
<tr>
<td>23</td>
<td>Polycarboxylate Polymers as Used in Detergents</td>
<td>November 1993</td>
</tr>
<tr>
<td>24</td>
<td>Pentafluoroethane</td>
<td>May 1994</td>
</tr>
<tr>
<td>25</td>
<td>1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124)</td>
<td>July 1994</td>
</tr>
<tr>
<td>26</td>
<td>Linear Polydimethylsiloxanes (CAS No. 63148-62-9)</td>
<td>September 1994</td>
</tr>
<tr>
<td>27</td>
<td>n-Butyl Acrylate</td>
<td>August 1994</td>
</tr>
</tbody>
</table>
No. 28 Ethyl Acrylate (CAS No. 140-88-5) (Published September 1994)
No. 29 1,1-Dichloro-1-fluoroethane (HCFC-141b) (CAS No. 1717-00-6) (Published December 1994)
No. 30 Methyl Methacrylate (CAS No. 80-62-6) (Published February 1995)
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No. 36 n-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9) (Published December 1996)
No. 37 Methyl Acrylate (CAS No. 96-33-3) (Published September 1998)
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No. 42 Tetrafluoroethylene (CAS No. 116-14-3) (Published December 2003)
No. 43 sec-Butanol (CAS No. 78-92-2) (Published March 2004)
No. 44 1, 1, 1, 3, 3-Pentafluoropropane (HFC-245fa) (Published June 2004)
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