



***1,1-Difluoroethane (HFC-152a)***  
***(CAS No. 75-37-6)***

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## **ECETOC JACC REPORT No. 45**

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## EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the toxicity and ecotoxicity data on 1,1-difluoroethane (HFC-152a), including results of recent and unpublished toxicological studies conducted under the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT)<sup>a</sup>.

HFC-152a, a colourless, flammable gas, is used as a non-ozone depleting aerosol propellant and an alternative to trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) in foam applications. In the atmosphere, HFC-152a degrades by photo-oxidation over a lifetime of 1.5 years, ultimately yielding carbon monoxide, carbon dioxide and hydrogen fluoride. Its global warming potential is 140 compared to carbon dioxide for an integration time horizon of 100 years.

In experimental animals HFC-152a possesses a low order of acute inhalation toxicity, although it can induce cardiac sensitisation at high exposure levels (150,000 ppm, 405,000 mg/m<sup>3</sup>). HFC-152a was not toxic or carcinogenic in a long-term (2-year) inhalation study in which up to 25,000 ppm (67,500 mg/m<sup>3</sup>) was administered to rats. HFC-152a did not cause any developmental effects at 50,000 ppm (135,000 mg/m<sup>3</sup>), the highest level tested.

In genetic testing, HFC-152a was not mutagenic in bacteria (Ames assay). HFC-152a caused chromosome aberrations in cultured human lymphocytes, but only after continuous treatment for 19 hours. The response was considered to be of marginal biological relevance. No micronuclei were found in rats exposed (*in vivo*) to 19,500 ppm (52,700 mg/m<sup>3</sup>).

In the absence of measured data, bioaccumulation and toxicity in aquatic organisms are predicted to be low.

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<sup>a</sup> A co-operative programme (1987 - 2000) sponsored by 16 leading chlorofluorocarbon producers [<http://www.afeas.org/paft/>]

## 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-difluoroethane (HFC-152a) (CAS No. 75-37-6).

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-Difluoroethane (HFC-152a <sup>a</sup>), is a colourless, flammable gas with a slight ethereal odour, is used as a non-ozone depleting aerosol propellant and as an alternative to trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) in foam applications.

HFC-152a has a low order of acute toxicity. There were no deaths in rats exposed by inhalation to a concentration of 319,000 ppm (861,000 mg/m<sup>3</sup>) for 4 hours. In another 4-hour inhalation study in rats, the approximate lethal concentration was 383,000 ppm (1,034,000 mg/m<sup>3</sup>).

HFC-152a has been evaluated for its potential to cause cardiac sensitisation in dogs given injections of epinephrine (adrenaline) while breathing atmospheres containing 50,000 and 150,000 ppm HFC-152a (135,000 and 405,000 mg/m<sup>3</sup>). Three of 12 dogs exposed to 150,000 ppm HFC-152a developed cardiac arrhythmias; there were no such effects at 50,000 ppm. The no-observed adverse effect level (NOAEL) was thus 50,000 ppm.

Repeated exposure of rats to vapours of HFC-152a at concentrations of up to 25,000 ppm (67,500 mg/m<sup>3</sup>) for 2 years revealed no clear evidence of toxicity or carcinogenicity.

In developmental toxicity studies with rats, HFC-152a was not teratogenic and did not cause foetal effects at inhalation concentrations of up to 50,000 ppm (135,000 mg/m<sup>3</sup>).

HFC-152a was not mutagenic in *Salmonella typhimurium* (Ames assay) and *Escherichia coli*. In an *in vitro* chromosome aberration assay with human lymphocytes, HFC-152a showed statistically significant evidence of clastogenic activity, but only after continuous 19-hour treatment in the absence of metabolic activation. Moreover, the observed positive response was weak and was considered to be of marginal biological relevance. HFC-152a was not active in a micronucleus assay in which rats were exposed to 19,500 ppm (52,700 mg/m<sup>3</sup>).

HFC-152a is expected to enter the ambient atmosphere if released into the environment. Its global warming potential (GWP) is 140 relative to CO<sub>2</sub>. HFC-152a is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals with an atmospheric lifetime of 1.50 years (half-life 1.04 years). The degradation products are, ultimately, CO, CO<sub>2</sub> and hydrogen fluoride (HF). In water, HFC-152a is not expected to adsorb to sediment or particulate matter or to volatilise rapidly from water surfaces. Bioconcentration is expected to be low, based on an estimated bioconcentration factor (BCF) value of 2. The predicted toxicity of HFC-152a to aquatic organisms is low.

The American Industrial Hygiene Associations' Workplace Environmental Exposure Level Committee has established a permissible exposure limit for HFC-152a of 1,000 ppm (2,700 mg/m<sup>3</sup>) as an 8-hour time-weighted average.

<sup>a</sup> The naming and numbering system for fluorocarbons is explained in Appendix B

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

### 2.1 Identity

Name: 1,1-Difluoroethane

IUPAC name: 1,1-Difluoroethane

Synonyms: HFA-152a  
HFC-152a  
R-152a

CAS name: 1,1-Difluoroethane

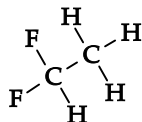
CAS registry number: 75-37-6

EC (EINECS) number: 200-866-1

Formula: C<sub>2</sub>H<sub>4</sub>F<sub>2</sub>

Molecular mass: 66.05

Structural formula:



### 2.2 EC classification and labelling

1,1-Difluoroethane (HFC-152a) is not classifiable as a dangerous substance according to the Dangerous Substances Directive 67/548/EEC and its subsequent amendments (EC, 2001).

### 2.3 Physical and chemical properties

HFC-152a is a colourless, flammable gas at room temperature and normal atmospheric pressure. It has a slight ethereal odour and is slightly soluble in water. Physical and chemical properties are given in Table 1.



**Table 1: Physical and chemical properties**

Property	Value, unit	Reference
Melting point	-117°C	Lewis, 1997
Boiling point at 1,013 hPa	-25°C	Lewis, 1997; Du Pont, 1998
Relative density of liquid, $D_4^{25}$ (density of water at 4°C is 1,000 kg/m <sup>3</sup> )	0.90 <sup>a</sup>	Du Pont, 1998
Viscosity at 20°C	No data	
Refractive index $n_D$ at 20°C	No data	
Vapour pressure at 25°C	6,067 hPa <sup>b</sup> 6,000 hPa <sup>c</sup>	Daubert and Danner, 1989 Du Pont, 1998
Vapour density at 25°C (air = 1)	2.4	Du Pont, 1998
Threshold odour concentration	No data	
Surface tension at 20°C	No data	
Solubility in water at 25°C	2.8 g/l <sup>d</sup>	Du Pont, 1998, 2000a
Miscible with acetone, ethanol and petroleum solvents	No data	
Partition coefficient, log $K_{ow}$ (octanol/water) at 20°C	0.49 0.75 <sup>f</sup>	Calculated <sup>e</sup> Hansch and Leo, 1995 cited by HSDB, 2001
Partition coefficient, log $K_{oc}$ (organic carbon/water) at 20°C	No data	
Henry's Law constant at 25°C	2,390 Pa·m <sup>3</sup> /mol	Calculated <sup>g</sup>
Flash point (closed cup), flammability limits at 20 - 25°C	< -50°C, 3.9 - 16.9% (v/v)	Du Pont, 1998, 2000a
Explosion limits in air at 1,013 hPa, at ambient temperature	No data	
Auto-flammability, ignition temperature	454°C	Du Pont, 1998

<sup>a</sup> Reported as 0.90 g/cc

<sup>b</sup> Reported as 4,550 mm Hg

<sup>c</sup> Reported as 87 psia (pounds/inch<sup>2</sup>) absolute pressure; 1 bar = 1,000 hPa = 14.5 psia

<sup>d</sup> Reported as 0.28% (w/w); 1 atm of gaseous HFC-152a in equilibrium with water

<sup>e</sup> According to Meylan and Howard, 1995

<sup>f</sup> Measured;

<sup>g</sup> Molecular mass x 1 atm/solubility in water at 1 atm

Typically, commercial HFC-152a has a purity of  $\geq 99.9\%$ . Trace level impurities may include propylene, fluoroethane, methane and various hydrocarbons, depending on the conditions of the production process (Section 3.1).

## ***2.4 Conversion factors***

Conversion factors for HFC-152a concentrations in air at 25°C and 1,013 hPa are:

- 1 ppm = 2.700 mg/m<sup>3</sup>
- 1 mg/m<sup>3</sup> = 0.370 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 = 2.746 mg/m<sup>3</sup> and 1 mg/m<sup>3</sup> = 0.364 ppm.

## ***2.5 Analytical methods***

HFC-152a has been analysed (in workplace air) using a gas chromatograph (GC) equipped with a flame ionisation detector (FID). In this method the gas sample (1 ml) is injected into the heated (200°C) port of a packed column and separated at 100°C isothermal (helium carrier gas). The limit of detection of the method is estimated to be 0.1 ppm (0.27 mg/m<sup>3</sup>) (Du Pont, 2001a).

There are no specific standard methods for the analysis of low concentrations of HFC-152a in ambient air and water.

### 3. PRODUCTION, STORAGE, TRANSPORT AND USE

#### 3.1 Production

HFC-152a is prepared by the reaction of hydrogen chloride (HCl), HF and chloroethylene (vinyl chloride, C<sub>2</sub>H<sub>3</sub>Cl) in the presence of a tin chloride (SnCl<sub>4</sub>) catalyst, followed by reaction of the products with liquid phase HF. HFC-152a is recovered from the process stream and volatiles remaining in the liquid phase are purged by bubbling through nitrogen. A process reaction time of 8.75 hours yields approximately 81 molar percent (Nappa and Wuttke, 1997).

Annual global production is estimated to be approximately 45 x 10<sup>6</sup> pounds (20.4 kt)<sup>a</sup> (Creazzo, 2003).

#### 3.2 Storage

HFC-152a (liquefied) is stored in cylinders equipped with temperature and pressure relief valves. The cylinders are kept in a clean, dry, ventilated area at temperatures below 52°C. Respiratory protection is not normally required.

Although stable, HFC-152a is a flammable gas with a lower flammability limit of 3.9% (Table 1); contact with open flames and high temperatures must thus be avoided. HFC-152a will form HF and possibly carbonyl fluoride (COF<sub>2</sub>) on decomposition. To avoid sources of ignition, the cylinders are grounded and material handled using explosion-proof equipment and fire protective clothing with antistatic control.

HFC-152a is incompatible with alkali metals, alkaline earth metals or powdered metals such as Al, Zn and Be (Du Pont, 1998).

#### 3.3 Transport and handling

HFC-152a can be transported as a liquefied gas in cylinders or tanks as aircraft cargo only. According to the US Department of Trade (DOT), HFC-152a is classified as a flammable gas (UN No.1030, Class 2.2) (Du Pont, 1998).

In Germany, HFC-152a is classified as a low hazard to water (Wassergefährdungsklasse, WGK 1) (Umweltbundesamt, 2003).

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<sup>a</sup> 1 pound = 1 lb = 0.4535924 kg

### ***3.4 Use***

The primary uses for HFC-152a are as an aerosol propellant and as an alternative to trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) in foam expansion. Other potential uses include refrigeration blends and catalyst regeneration. Global use is estimated to equal production (Section 3.1) (Creazzo, 2003).

## 4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

### 4.1 Emissions

#### 4.1.1 Natural sources

There is no known natural source of HFC-152a.

#### 4.1.2 Emissions during production and use

There are no quantitative data on the emission of HFC-152a from manufacturing facilities.

Since HFC-152a is used as a propellant and foaming agent, it will primarily be emitted to the atmosphere. No quantitative data are available.

### 4.2 Environmental distribution

The environmental partitioning of HFC-152a 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-152a using the physical properties given in Table 1 and an atmospheric lifetime of 1.04 years (Section 4.3.1). Degradation in other media was not taken into account. Table 2 below gives the percentage of HFC-152a calculated to be present in each compartment.

**Table 2: Partitioning (%) into the environment (Franklin, 2003)**

Compartment	EQC Level I	EQC Level III	
		Emission to air alone	Emission to water alone
Air	99.79	99.84	19.7
Water	0.21	0.15	80.2
Soil	0.001	0.010	0.002
Sediment	0.00002	0.0003	0.17

The Level III simulation with emissions of HFC-152a 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-152a 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.

### 4.3 Environmental fate and biotransformation

#### 4.3.1 Atmospheric fate and impact

##### *Lifetime*<sup>a</sup>

The atmospheric degradation of HFC-152a occurs mainly in the troposphere, being initiated by reaction with naturally occurring hydroxyl radicals (photo-oxidation). HFC-152a is not expected to undergo significant hydrolysis or direct photolysis in the troposphere due to the lack of reactive functional groups to hydrolyse and its inability to absorb UV radiation at environmentally significant wavelengths.

The Intergovernmental Panel on Climate Change (IPCC) has estimated the overall atmospheric lifetime of HFC-152a to be 1.50 y (548 days), corresponding to a half-life of 1.04 years (380 days) (IPCC, 1996). Although IPCC (2001) gives a slightly different value (1.4 years or 511 days, corresponding to a half-life of 0.99 years or 354 days), the IPCC (1996) value has been adopted for calculating the GWP used for regulatory purposes under the Kyoto Protocol (see below).

##### *Ozone depleting potential*

HFC-152a contains neither chlorine nor bromine, its ozone depleting potential is zero.

<sup>a</sup> Lifetime is the time necessary for 63% degradation: it is equal to the "half-life" divided by  $\ln 2$  (= 0.69)

### *Global warming potential*

The GWP of a greenhouse gas 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. CO<sub>2</sub>) or infinite (e.g. CFC-11). Almost invariably, GWP values are expressed relative to CO<sub>2</sub>, for an ITH of 100 years.

The estimated 100-year GWP of HFC-152a is 140, relative to a value of 1.0 for CO<sub>2</sub> (IPCC, 1996). This is the value to be used for the regulation of greenhouse gases under the Kyoto Protocol.

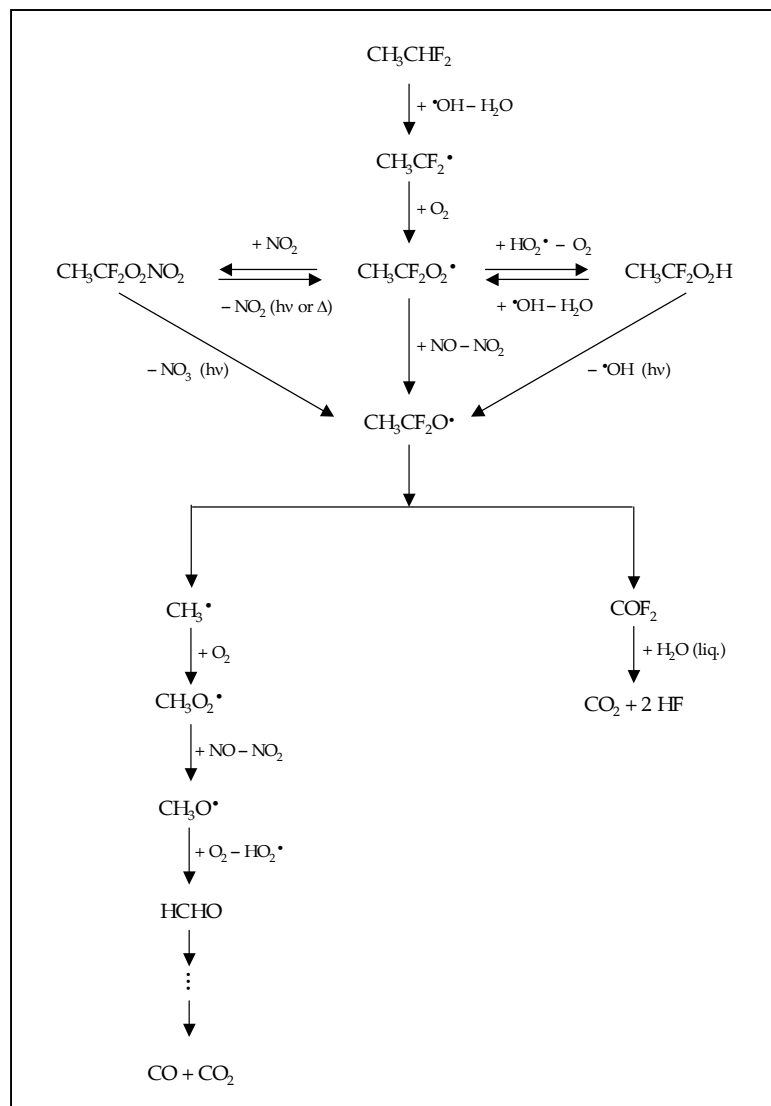
### *Tropospheric ozone formation*

As discussed by Niki (1989) and Hayman and Derwent (1997), HFC-152a is too unreactive in the atmosphere to make any significant contribution to tropospheric ozone formation and the related photochemical smog, near the emission sources (particularly in urban areas).

The US Environmental Protection Agency has excluded HFC-152a as a volatile organic compound from its ozone control programme (US-EPA, 1997).

### *Degradation mechanism and products*

A reaction scheme for the degradation of HFC-152a in the troposphere is proposed in Figure 1. This scheme is based on the general mechanisms developed by Atkinson *et al* (1989), on those elucidated for a large number of HCFCs and HFCs since the late 1980s (Cox *et al*, 1995; Lelieveld *et al*, 1999), and on specific studies on HFC-152a (Edney and Driscoll, 1992; Tuazon and Atkinson, 1993a,b; Chen *et al*, 1996).

**Figure 1: Tropospheric degradation mechanism for HFC-152<sup>a</sup>**

<sup>a</sup> NO<sub>2</sub>, NO and NO<sub>3</sub>, free radicals

According to the scheme presented in Figure 1, the principal ultimate degradation products of HFC-152a are CO, CO<sub>2</sub> and HF, with formaldehyde (HCHO) and COF<sub>2</sub> as the main non-radical intermediates. The scheme assumes that the initial attack on HFC-152a by hydroxyl radicals leads to abstraction of the hydrogen atom principally from the CHF<sub>2</sub>- group, rather than from the CH<sub>3</sub>- group. This has been shown to be the case (99% regio-selectivity) for the analogous abstraction of hydrogen by chlorine atoms (Tuazon and Atkinson, 1993a,b).

The peroxyxynitrate CH<sub>3</sub>CF<sub>2</sub>O<sub>2</sub>NO<sub>2</sub> and the hydroperoxide CH<sub>3</sub>CF<sub>2</sub>O<sub>2</sub>H are believed to be rather short-lived intermediates, undergoing photolysis, thermal decomposition or reaction with



hydroxyl radicals, leading to the regeneration of peroxy radicals ( $\text{CH}_3\text{CF}_2\text{O}_2^\bullet$ ) or the formation of alkoxy radicals ( $\text{CH}_3\text{CF}_2\text{O}^\bullet$ ) (Cox *et al*, 1995; Lelieveld *et al*, 1999).

The  $\text{COF}_2$  formed as an intermediate will be taken up by cloud droplets, on a timescale of days to weeks, and hydrolysed to  $\text{CO}_2$  and HF (Cox *et al*, 1995).

#### 4.3.2 Aquatic fate

No data are available.

By analogy with similar compounds (Zoeteman *et al*, 1980), any HFC-152a that might be present in aqueous waste streams discharged directly into rivers or lakes would be expected to have a half-life with respect to volatilisation of days or at most a few weeks. The estimated half-lives for a model river (depth 1 m, flow 1 m/s, wind velocity 3 m/s) and a model lake (depth 1 m, flow 0.05 m/s, wind velocity 0.5 m/s) are 2 and 77 hours, respectively (Lyman *et al*, 1990; SRC, n.d.; both cited by US-EPA, 2001).

#### 4.3.3 Terrestrial fate

No data are available.

#### 4.3.4 Biodegradation

No data are available.

#### 4.3.5 Bioaccumulation

No data are available.

A bioconcentration factor (BCF) of 2 has been based on a measured log  $K_{ow}$  of 0.75 (Table 1) and a recommended regression-derived equation (Lyman *et al*, 1990 cited by US-EPA, 2001). According to a classification scheme (Franke *et al*, 1994 cited by HSDB, 2001), the estimated BCF value of 2 suggests that bioconcentration in aquatic organisms is low.

## 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

### 5.1 *Environmental levels*

In 1998 and 2000, HFC-152a concentrations of 1.3 ppt and 1.7 ppt (v/v), respectively, were observed in the background atmosphere (WMO, 2002).

### 5.2 *Human exposure levels and hygiene standards*

#### 5.2.1 **Non-occupational exposure**

No direct measurements have been made of consumer exposure to HFC-152a.

Using data and simulations from dimethylether (DME) and other propellants, consumers would receive a potential dose of less than 1.62 mg DME/kg/d or, adjusting for molecular weight, 2.32 mg HFC-152a/kg/d (Du Pont, 2001b).

#### 5.2.2 **Occupational exposure**

No industrial hygiene monitoring data are available.

Based on modelling and simulation of institutional/commercial exposure to propellants, worker exposure has been estimated to be 5,890 ppm-min/d, equivalent to a maximum potential dose of 2.69 mg DME/kg/d or 3.86 mg HFC-152a/kg/d. The average exposure level was approximately 10 ppm (27 mg/m<sup>3</sup>) (Du Pont, 2001b).

#### 5.2.3 **Hygiene standards**

The American Industrial Hygiene Association has established a workplace environmental exposure level (WEEL) of 1,000 ppm (2,700 mg/m<sup>3</sup>) for HFC-152a as an 8-hour time-weighted average concentration (AIHA, 1994).

## 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

### 6.1 Micro-organisms

No data are available.

### 6.2 Aquatic organisms

No data are available.

ECOSAR (US-EPA, 2000; CoR 2f) was used to predict the aquatic toxicity of HFC-152a to green algae, daphnids (planktonic freshwater crustaceans) and fish (Table 3). The log  $K_{ow}$  used for the calculations was 0.75 (Table 1). ECOSAR predictions are based on toxicity data generated on classes of compounds with similar modes of action (i.e. narcosis for fluorocarbons).

**Table 3: Predicted acute toxicity to aquatic organisms**

Organism	Duration	Effect/ Parameter	Concentration (mg/l)
Green alga	96 h	<b>Growth inhibition</b> EC <sub>50</sub>	419
Daphnid	48 h	<b>Immobility</b> EC <sub>50</sub>	720
Fish	96 h	<b>Lethality</b> LC <sub>50</sub>	733

The predicted values indicate that HFC-152a will have a low order of toxicity to aquatic organisms.

### 6.3 Terrestrial organisms

No data are available.

### 6.4 Ecosystems

No data are available.

## 7. KINETICS AND METABOLISM

### 7.1 *Body distribution*

No data are available.

### 7.2 *In vitro metabolism*

No data are available.

### 7.3 *In vivo metabolism*

Male Crl:CD BR rats (3/group) were exposed to HFC-152a in a gas uptake chamber at concentrations of 370, 470, 1,500 or 2,650 ppm (1,000, 1,270, 4,050 or 7,160 mg/m<sup>3</sup>) for 4 hours. HFC-152a was metabolised by oxidation at a slow but measurable rate, with kinetic constants V<sub>max</sub> and K<sub>m</sub> assigned values of 7.8 mg/h/kgbw and 27.9 mg/l respectively. Fluoride ion and trace acyl fluoride were identified as urinary metabolites (Du Pont, 1994). As determined by physiologically-based pharmacokinetic modelling techniques, HFC-152a metabolism will become saturated at exposure concentrations of approximately 75,000 ppm (203,000 mg/m<sup>3</sup>) (Keller, 1995).

## 8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

### 8.1 Acute toxicity

#### 8.1.1 Oral

An approximate lethal dose study was conducted in male Crl:CD BR rats, with dose levels of 200, 300, 450, 670, 1,000 or 1,500 mg HFC-152a/kgbw dissolved in corn oil. Doses of 450 mg/kgbw and above were administered as 2 portions, at about 15 minute intervals; 1,500 mg/kgbw was the maximum feasible dose. Rats were observed for mortality, clinical signs, and body-weight changes over a 14-day period. No mortality occurred at any dose level. Immediately after dosing, abdominal distension related to gas evolution was evident in all rats, and lethargy was observed at 1,000 and above. High carriage, wet and yellow stained perineum, and diarrhoea were observed in all rats 1 to 2 days post-dosing. There were no other toxicologically significant effects (Malek, 1990; CoR 3b).

#### 8.1.2 Dermal

No data are available.

#### 8.1.3 Inhalation

Charles River CD rats (6 males/group) were exposed (whole-body) to 66,400, 175,200, 319,000, 383,000 or 437,500 ppm HFC-152a (179,300, 473,000, 861,000, 1,034,000 or 1,181,000 mg/m<sup>3</sup>) for 4 hours. Oxygen levels were maintained at about 20% for exposures at or above 319,000 ppm. After a 14-day observation period, gross pathology was performed on surviving rats. Laboured breathing, lethargy, and unresponsiveness to sound were observed during exposure. Mortality occurred at 383,000 and 437,500 ppm, in 1 and 2 rats respectively. There were no clinical signs or compound-related gross pathology changes. The approximate 4-hour lethal concentration was determined to be 383,000 ppm (1,034,000 mg/m<sup>3</sup>) (Moore and Trochimowitz, 1975; CoR 1d).

#### 8.1.4 Other studies

Male beagle dogs (12/group) of unspecified age were exposed to 50,000 ppm or 150,000 ppm HFC-152a (135,000 or 405,000 mg/m<sup>3</sup>) for 5 minutes. The dogs received a control injection of epinephrine (adrenaline) (0.008 mg/kgbw intravenously) prior to exposure and a challenge injection (same dose) at the end of the exposure period. Marked cardiac arrhythmia, considered to pose a serious threat to life, was observed in 3 dogs at 150,000 ppm; no response was seen at 50,000 ppm (135,000 mg/m<sup>3</sup>) (Reinhardt *et al*, 1971; CoR 2e).

Other studies have been reported using anaesthetised mice (Aviado and Belej, 1974; Brody *et al* 1974; Doherty and Aviado 1975; all CoR 3c). The use of anaesthetised animals in cardiac sensitisation studies is not consistent with the regulatory required test protocol.

## **8.2 Skin, respiratory tract and eye irritation, sensitisation**

HFC-152a is a gas at room temperature and thus no specific test data are available on these endpoints.

There was no evidence of skin or eye irritation in rats exposed, whole-body, to HFC-152a for 2 years (McAlack and Schneider, 1982; CoR 4e) (Section 8.5).

## **8.3 Repeated dose toxicity**

During a 2-year inhalation study in rats, there were no adverse effects in the animals at the 3-month *interim* kill. The NOAEL was 25,000 ppm (67,500 mg/m<sup>3</sup>) (McAlack and Schneider, 1982; Pathology Associates, 1992; both CoR 1a) (Section 8.5).

## **8.4 Genotoxicity**

### **8.4.1 In vitro**

HFC-152a was not mutagenic when tested in *Salmonella typhimurium* and *Escherichia coli*, both with and without S9<sup>a</sup> metabolic activation (Table 4).

Two *in vitro* chromosomal aberration tests were conducted using human lymphocytes. In the first, a 3-hour exposure in the presence or absence of S9, HFC-152a caused no biologically-relevant statistically-significant increases in the proportion of cells with chromosomal aberrations at any dose level. In a confirmatory 19-hour exposure in the absence of S9, there was a statistically significant increase at the 70% dose level in the proportion of cells with chromosomal aberrations (excluding gap-type aberrations). In the presence of S9, HFC-152a caused no statistically significant increase in the proportion of metaphase figures containing chromosomal aberrations at any dose level. In the second study, cultures treated with 50 and 70% HFC-152a did not show any statistically significant increases in chromosome aberrations. No increases in the proportion of polyploid cells were seen in cultures treated with the negative control and highest dose level. All positive controls caused large, statistically significant increases in the proportion of aberrant cells, demonstrating the sensitivity of the test system and the efficacy of the S-9 mix. The weak but statistically significant evidence of clastogenic activity after continuous 19-hour treatment in the absence of S9 was considered to be of marginal biological relevance (Du Pont, 2000b) (Table 4).

<sup>a</sup> Supernatant of centrifuged 9,000 x g liver homogenate, containing the microsome and cytosol fractions, derived from rats previously treated with Aroclor to induce microsomal enzyme activity

**Table 4: Genotoxicity In Vitro**

Species, strain	Protocol	Endpoint	Metabolic activation	Vapour concentration		Result	Reference	CoR
				%	(mg/m <sup>3</sup> ) <sup>a</sup>			
<i>Salmonella typhimurium</i> , TA97a, TA98, TA100, TA1535	Standard agar	Reverse mutation	+/- S9	0	0	-ve	Gladnick, 2000	1a
				20	540,000			
				30	810,000			
				40	1,080,000			
				50	1,350,000			
				75	2,030,000			
<i>Escherichia coli</i> , WP2uvrA (pKM101)	Standard agar	Reverse mutation	+/- S9	0	0	-ve	Gladnick, 2000	1a
				20	540,000			
				30	810,000			
				40	1,080,000			
				50	1,350,000			
				75	2,030,000			
Human lymphocytes	OECD 473	Chromosome aberration	+/- S9	0	0	Weakly +ve <sup>b</sup>	Du Pont, 2000b	1a
				35	945,000			
				50	1,350,000			
				60	1,620,000			
				70	1,890,000			

<sup>a</sup> Converted values<sup>b</sup> Marginal biological relevance

#### 8.4.2 In vivo chromosome damage assays

In a micronucleus test, rats exposed (whole-body) to HFC-152a vapour show no evidence of chromosome damage or bone marrow cell toxicity (Table 5).

In a sex-linked recessive lethal test conducted in fruit flies (*Drosophila melanogaster*), one heterozygous female exposed to 100% HFC-152a (98% pure) had ocelli in place of a proboscis. Eye colour mutants transmitted were white, apricot, and a deep orange (Table 5). The lack of explanation and documentation render this study insufficient for assessment.

**Table 5: In vivo chromosome damage tests**

Species, strain, number, sex/group	Protocol, endpoint	Endpoint	Exposure time	Vapour concentration		Result	Reference	CoR
				(ppm)	(mg/m <sup>3</sup> ) <sup>a</sup>			
Rat, Sprague-Dawley CD, 5M, 5F	OECD 474	Micronuclei	6 h	0	0	-ve	Du Pont, 2001c	1a
				4,875	13,160			
				9,750	26,330			
				19,500	52,700			
<i>Drosophila melanogaster</i> Canton-S, 276 F	Basic	Mutations	5 min	1,000,000 <sup>b</sup>	2,700,000	+ve	Foltz and Fuerst, 1974	3a

<sup>a</sup> Converted values<sup>b</sup> Reported as 100%

### 8.5 Chronic toxicity and carcinogenicity

CrI:CD BR rats (120/sex/group) were exposed (6 h/d, 5 d/wk) by inhalation (whole-body) to 0, 2,000, 10,000 or 25,000 ppm HFC-152a (0, 5,400, 27,000, 67,500 mg/m<sup>3</sup>) for 2 years. Mean body weights and body weight gains of male and female rats were comparable or superior to their respective controls. At 25,000 ppm, ocular/nasal discharges and wet/stained perinea were observed in males and females, and stained body and/or face in females only. The latter two effects were dose-related. The incidence of swollen ears was significantly elevated in the 2,000 ppm males and the 25,000 ppm males and females, with a dose-related trend apparent in the females. At the time of final kill, mortality ratios in the 0, 2,000, 10,000 and 25,000 ppm groups were 48/100, 51/100, 49/100 and 51/100 in males, and 54/100, 61/100, 47/100 and 47/100 in females, respectively. Over the duration of the study, female rats exposed to 10,000 and 25,000 ppm exhibited increased mean corpuscular volumes and increased serum bilirubin in all treatment groups, while male rats at those two levels exhibited increased haematocrit levels and increased mean corpuscular volumes, and at 25,000 ppm only, increased urobilinogen. In the absence of any abnormalities in haematopoietic tissues or in red blood cell counts among either males or females or of changes in serum bilirubin in males, the above observations provide inconclusive evidence of a haemolytic effect. Absolute numbers of eosinophils were significantly lower only for the 10,000 ppm females, but relative to body weight were significantly lower for all groups. Relative and absolute numbers of monocytes were significantly lower than control values for all treated males. The depression in monocytes is of unknown clinical or biological significance. There was a dose-related increase in urinary fluoride concentration in the 10,000 and 25,000 ppm males and females and in the 2,000 ppm males when evaluated over the entire study. Serum creatinine was significantly elevated in both the 10,000 and 25,000 ppm females. The latter also exhibited increased urinary volume and decreased urine osmolality. A difference in organ weights was noted at 3 months (McAlack and Schneider, 1982; CoR 1a). A peer review of the pathological findings revealed no distinct evidence of HFC-152a induced toxicity or carcinogenicity in any tissue examined (Pathology Associates, 1992; CoR 1a).



## 8.6 Reproductive toxicity, embryotoxicity and teratology

### 8.6.1 Reproductive toxicity

In the 2-year inhalation study described above (Section 8.5) 10 rats/sex/group were necropsied at 3 and 12 months, and all surviving rats at 24 months. Gross examination was conducted on all rats and microscopic examinations on the control and high-exposure groups and on any animals that died or were killed *in extremis*. Reproductive organs evaluated histopathologically included testis, epididymis, prostate, ovary, uterus, and vagina. The testes were weighed and their mean organ to final body weight ratios calculated. There were no gross or histopathological effects on the reproductive organs of either male or female rats (McAlack and Schneider, 1982; CoR 2e).

### 8.6.2 Embryotoxicity and teratology

Charles River CD rats (27 F/group) were exposed (6 h/d) by inhalation (whole body) to 0, 5,000 or 50,000 ppm HFC-152a (0, 13,500 or 135,000 mg/m<sup>3</sup>) on days 6 to 15 of gestation (cesarean section on day 21). Dams were killed on day 21, organs of the thoracic and abdominal cavities examined, and uterine weight recorded. *Corpora lutea*, implantation sites, live and dead fetuses, resorptions, foetal weight, crown-rump length of live fetuses, and a gross external foetal examination were also recorded. Approximately half of the number of fetuses from each litter were examined for skeletal abnormalities and the remaining fetuses examined for visceral and neural anomalies. No compound-related clinical signs of maternal toxicity or body weight changes were observed. There were no gross pathological abnormalities in ovaries, uterine horns, vital organs, or tissues of treated animals. Pregnancy ratios at 0, 5,000, and 50,000 ppm were 22/27, 21/27 and 19/27, respectively. The NOAEL for maternal and developmental toxicity was 50,000 ppm (135,000 mg/m<sup>3</sup>), the highest level tested (Du Pont, 1979; CoR 1d).

A summary of other reproductive outcomes of this study is provided in Table 6.

**Table 6: Other reproductive outcomes<sup>a</sup> (Du Pont, 1979)**

Concentration (ppm)	0	5,000	50,000
<i>Corpora lutea</i>	11.6	11.3	12.2
Implantations	10.0	9.4	10.5
Number of resorptions	1.5	1.4	1.2
Total number of fetuses <sup>b</sup>	9.3	8.8	9.9
Total number of live fetuses <sup>b</sup>	9.3	8.8	9.9
Mean foetal weight (g)	4.3	4.4	4.3

<sup>a</sup> Mean/litter

<sup>b</sup> Sex not recorded

The number of *corpora lutea*, implantation sites, and live foetuses per litter was similar in all groups. The post-implantation death of fertilised ova in exposed females (indicated by early and late resorptions and dead foetuses) was similar to that of controls. In all groups, foetal body measurements, i.e. mean weight and crown-rump length, were similar to controls. HFC-152a treatment had no effect on embryonal development (as measured by gross external, visceral, and skeletal examinations). The number of petechial haemorrhages and small subcutaneous haematomas on various parts of the body was similar in all groups, as was the number of runts among litters and foetuses. Apparent hydronephrosis, transposition of the viscera, liver peliosis, and internal haemorrhage were detected. None of these findings were considered to be treatment related. Skeletal changes (minor anomalies and variants) were about equally distributed in all groups. A summary of gross, soft tissue, and skeletal anomalies is provided in Table 7.

**Table 7: Gross, soft tissue and skeletal anomalies<sup>a</sup> (Du Pont, 1979)**

	Concentration (ppm)		
	0	5,000	50,000
<b>Gross external</b> (number examined)	22 (205)	20 (184)	19 (188)
Petechial haemorrhages	4 (4)	5 (5)	3 (5)
Haematoma	10 (12)	6 (7)	8 (14)
Runts	2 (2)	1 (1)	1 (1)
<b>Soft tissue</b> (number examined)	22 (105)	20 (93)	19 (90)
Hydronephrosis (apparent)	1 (1)	3 (4)	2 (2)
<i>Situs inversus</i>	0	0	1 (1)
Liver peliosis	0	0	3 (3)
Internal haemorrhage	1 (1)	0	0
<b>Skeletal</b> (number examined)	22 (100)	20 (91)	19 (98)
14 <sup>th</sup> rudimentary rib	16 (51)	16 (53)	19 (69)
Wavy ribs	8 (17)	6 (8)	5 (7)
Sternebrae unossified	10 (14)	9 (16)	12 (23)
Bipartite centra	3 (3)	0	2 (2)
Hyoid unossified	2 (3)	0	4 (6)

<sup>a</sup> Number of litters (foetuses) affected

## 9. EFFECTS ON HUMANS

There are no reports of adverse health effects associated with the occupational or consumer use of HFC-152a.

A young woman burnt her hand after accidental ignition of gas from a compressed air duster filled with HFC-152a blowing agent. The symptoms reversed quickly and completely upon topical treatment with calcium gluconate gel, a first aid for HF burns (Section 3.2) (Foster *et al*, 2003).

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## APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

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

## 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", then 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  $\rightarrow$  C<sub>2</sub>F<sub>6</sub>
- HFC-23 = 3 Fs, 1 H, 1 C, and 0 Cls  $\rightarrow$  CF<sub>3</sub>H
- PFC-1216 = 6 Fs, 0 Hs, 3 Cs, 0 Cls with 1 double bond  $\rightarrow$  C<sub>3</sub>F<sub>6</sub>  $\rightarrow$  CF<sub>2</sub>=CF-CF<sub>3</sub>

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  $\rightarrow$  c-C<sub>4</sub>F<sub>8</sub>

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  $C_2H_2F_4$  can have two structural isomers:

- $CF_2H-CF_2H$ , more symmetrical, HFC-134
- $CF_3-CF_2H$ , 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 =  $CCl_2$
- b =  $CClF$
- c =  $CF_2$
- d =  $CClH$
- e =  $CHF$
- f =  $CH_2$

For example:

HFC-236fa =  $C_3F_6H_2$  → Central carbon designated "f" →  $CH_2$  → "a" designation →  $CF_3CH_2CF_3$

### ***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 = CCl<sub>3</sub>
- k = CCl<sub>2</sub>F
- l = CClF<sub>2</sub>
- m = CF<sub>3</sub>
- n = CHCl<sub>2</sub>
- o = CH<sub>2</sub>Cl
- p = CHF<sub>2</sub>
- q = CH<sub>2</sub>F
- r = CHClF
- s = CH<sub>3</sub>
- t = C
- x = CCl
- y = CF
- z = CH

Example: HFC-43-10mee = 10 Fs, 2 Hs, 5 Cs, no Cls → C<sub>5</sub>H<sub>2</sub>F<sub>10</sub>

m indicates CF<sub>3</sub> . . . CF<sub>3</sub>

e indicates CHF, so CF<sub>3</sub>CHF

e indicates CHF, so CF<sub>3</sub>CHFCHF

HFC-43-10mee → CF<sub>3</sub>CHFCHFCF<sub>2</sub>CF<sub>3</sub>

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 -CF<sub>2</sub>CF<sub>3</sub>).

## 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.

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

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

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

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

$$1 \text{ mg/m}^3 = 24.0556/Mw \text{ ppm} \dots\dots\dots(\text{Eq. B.3})$$

$$1 \text{ ppm} = Mw/24.0556 \text{ mg/m}^3 \dots\dots\dots(\text{Eq. B.4})$$

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

$$1 \text{ mg/m}^3 = 24.4661/Mw \text{ ppm} \dots\dots\dots(\text{Eq. B.5})$$

$$1 \text{ ppm} = Mw/24.4661 \text{ mg/m}^3 \dots\dots\dots(\text{Eq. B.6})$$

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No. 4	Hepatocarcinogenesis in Laboratory Rodents: Relevance for Man
No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology)
No. 6	Acute Toxicity Tests, LD <sub>50</sub> (LC <sub>50</sub> ) Determinations and Alternatives
No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies
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No. 13	DNA and Protein Adducts: Evaluation of their Use in Exposure Monitoring and Risk Assessment
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No. 20	Percutaneous Absorption
No. 21	Immunotoxicity: Hazard Identification and Risk Characterisation
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No. 5	Toxicity of Ethylene Oxide and its Relevance to Man
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| No. 9  | Chlorodifluoromethane   |
| No. 10 | Isophorone  |
| No. 11 | 1,2-Dichloro-1,1-difluoroethane (HFA-132b)                            |
| No. 12 | 1-Chloro-1,2,2,2-tetrafluoroethane (HFA-124) (updated by JACC No. 25) |
| No. 13 | 1,1-Dichloro-2,2,2-trifluoroethane (HFA-123) (updated by JACC No. 33) |
| No. 14 | 1-Chloro-2,2,2-trifluoromethane (HFA-133a)                            |
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| No. 24 | Pentafluoroethane (HFC-125) (CAS: 354-33-6)                           |

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No. 27 *n*-Butyl Acrylate (CAS No. 141-32-2)  
No. 28 Ethyl Acrylate (CAS No. 140-88-5)  
No. 29 1,1-Dichloro-1-fluoroethane (HCFC-141b) (CAS No. 1717-00-6)  
No. 30 Methyl Methacrylate (CAS No. 80-62-6)  
No. 31 1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)  
No. 32 Difluoromethane (HFC-32) (CAS No. 75-10-5)  
No. 33 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) (CAS No. 306-83-2)  
No. 34 Acrylic Acid (CAS No. 79-10-7)  
No. 35 Methacrylic Acid (CAS No. 79-41-4)  
No. 36 *n*-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9)  
No. 37 Methyl Acrylate (CAS No. 96-33-3)  
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| No. 11 | Ecotoxicology of some Inorganic Borates  |
| No. 12 | 1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0)            |
| No. 13 | Occupational Exposure Limits for Hydrocarbon Solvents                              |
| No. 14 | <i>n</i> -Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document       |
| No. 15 | Examination of a Proposed Skin Notation Strategy                                   |
| No. 16 | GREAT-ER User Manual   |
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No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction
No. 43	Contact Sensitisation: Classification According to Potency, A Commentary

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