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CAS No 1717-00-6

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ECETOC

Joint Assessment of Commodity Chemicals No. 29

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(HCFC-141b)

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December 1994

European Centre for Ecotoxicology
and Toxicology of Chemicals

Avenue E. Van Nieuwenhuyse 4, (Bte. 6)
B - 1160 Brussels, Belgium

ECETOC JACC Report No. 29

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to write reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a Producer, Government Official or Consumer can be informed on the up-to-date position with regard to safety, information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the reviewed assessed. To assist ourselves and others working in this field we publish annually a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report No. 30 entitled "Existing Chemicals: Literature Reviews and Evaluations".

This document is a revision of JACC report No. 15 published in August 1990 on 1,1 Dichloro-1-fluoroethane (HCFC 141b; CAS No. 1717-00-6). The text revisions introduce new environmental and toxicological data.

1,1-Dichloro-1-Fluoroethane (HCFC-141b) CAS No 1717-00-6

CONTENTS

SECTION 1. SUMMARY AND CONCLUSIONS

1,1-dichloro-1-fluoroethane (dichlorofluoroethane) is produced and used as a substitute for fully halogenated chlorofluorcarbons with comparable physical properties since it has more favourable environmental properties.

It is a volatile non flammable colourless liquid, with a weak ethereal odour and is slightly soluble in water. The low octanol/water partition coefficient (log P_{ow} = 2,3) indicates a low potential for bioaccumulation. The physical properties and results of acute ecotoxicity studies indicate that dichlorofluoroethane presents a low risk to the aquatic environment.

The overall atmospheric lifetime of dichlorofluoroethane is 10.8 years. Based on this lifetime the stratospheric ozone depletion potential (ODP) is 0.11 and the halocarbon global warming potential (HGWP) is 0.12 which is low compared with the fully halogenatedchlorofluoro-carbons such as trichlorofluoromethane (CFC 11) as reference which has an ODP and an HGWP of 1.0. The majority of the dichlorofluoroethane released to the environment degrades in the lower atmosphere, ultimately forming carbon dioxide and hydrochloric and hydrofluoric acids. At foreseable emission rates the degradation of dichlorofluoroethane will not contribute significantly to local tropospheric ozone formation or to the acidification of rainwater.

Studies in animals indicate that dichlorofluoroethane is easily absorbed via the respiratory route. Minimal metabolism of dichlorofluoroethane to 2,2-dichloro 2-fluoroethanol occurs. This metabolite is excreted in the urine of the rat in the form of its glucuronide conjugate.

Dichlorofluoroethane has a low order of acute toxicity. No mortality was observed in rats receiving oral doses of 5,000 mg/kg; only piloerection was noted. Dermal exposure of rats or rabbits to 2,000 mg/kg caused no mortality and no signs of toxicity.

Single exposure inhalation studies in mice indicate that the LC_{50} (30 min) was between 300,000 and 500,000 mg/m^3 (61,800 ppm and 103,000 ppm respectively) and the LC_{50} (4h) in rats was 300,700 mg/m^3 (62,000 ppm). Six hours exposure caused narcosis in mice at 198,850 mg/m^3 (41,000 ppm) and pre-narcotic signs were seen in mice and rats at levels higher than 145,500 mg/m^3 (30,000 ppm).

Liquid dichlorofluoroethane was not an irritant or a sensitising agent to skin, but may cause mild eye irritation.

No significant respiratory effects were seen in rats exposed to 48,500 mg/m^3 (10,000 ppm) dichlorofluoroethane for 25 minutes but at this concentration cardiac sensitisation to adrenaline could be induced in dogs and monkeys.

In repeated inhalation exposure studies, rats exposed 6 h/d, 5 d/wk, during periods ranging from 2 to 13 weeks the no-effect-level was considered to be 38,400 mg/m^3 (7,900 ppm). Concentration of 97,000 mg/m^3 (20,000 ppm) induced reduced alertness, reduced bodyweight gain and slightly increased levels of cholesterol, triglyceride and glucose.

No haematological and histopathological changes were noted.

There was no evidence of teratogenic or embryotoxic effects in pregnant rabbits exposed to 6,790, 20,370 or 61,110 mg/m^3 (1,400, 4,200 or 12,600 ppm) or in pregnant rats exposed to 15,520 or 38,800 mg/m^3 (3,200 or 7,900 ppm) of dichlorofluoroethane although signs of maternal toxicity were observed at and above 15,520 mg/m^3 (3,200 ppm) in rats and 20,370 mg/m^3 (4,200 ppm) in rabbits.

A two "generation" inhalation study in rats demonstrated a no-observed effect level of 38,800 mg/m^3 (8,000 ppm) for reproductive parameters. At a higher concentration, 97,000 mg/m^3 (20,000 ppm), a "non reproducible decrease" in the number of litters, in the number of pups per litter and also some retardation of sexual maturation of male pups which may have been caused by the slight body weight growth retardation, was observed.

Overall dichlorofluoroethane did not present toxicologically significant genotoxic activity *in vitro* and *in vivo.*

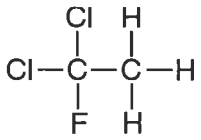
Rats were exposed by inhalation in a lifetime study to concentrations of 7,275, 24,250 and 97,000 mg/m^3 (1,500, 5,000 and 20,000 ppm). No significant evidence of toxicity was seen, however, at the highest exposure concentration reduced body weight gain was observed. Dichlorofluoroethane did not produce neoplastic changes in female rats at any test concentration. In male rats no neoplastic changes were noted at 7,275 mg/m^3 (1,500 ppm) but increased incidences of testicular interstitial cell (Leydig cells) hyperplasia and adenoma were observed at 24,250 (5,000 ppm) and 97,000 mg/m^3 (20,000 ppm). These changes appeared late-in life and were not correlated with increased mortality. Because of the non-genotoxicity of dichlorofluoroethane these effects on the rat Leydig cells are considered as to be of epigenetic origin and associated with senile endocrine disturbances, and therefore of no relevance to tumourigenic hazard for man.

There are no national permissible exposure limits but an occupational exposure limit (8h TWA) of 500 ppm (2,425 mg/m^3) has been established by AIHA for 1,1-dichloro-1-fluoroethane.

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

2.1 IDENTITY

Chemical structure:



Chemical formula: $CCl_2F\text{-}CH_3$

Common name: 1,1-Dichloro-1-fluoroethane
Dichlorofluoroethane

Common synonyms: Ethane 1,1-dichloro-1-fluoro
HFA 141b, HCFC 141b[1], R141b

Cas Registry Number: 1717-00-6

EINECS: not listed
ELINCS: listed
TSCA: listed

Conversion factors: 1 ppm = 4.85 mg/m^3 (20°C, 1013 hPa)
1 mg/m^3 = 0.206 ppm (20°C, 1013 hPa)

2.2 PHYSICAL AND CHEMICAL PROPERTIES

Dichlorofluoroethane is a non-flammable, volatile, colourless liquid at room temperature and normal atmospheric pressure, with a faint ethereal odour. It is slightly soluble in water. Some physical and chemical properties are given in Table 1.

[1] HCFC means Hydro-Chloro-Fluoro-Carbon: $C_2H_3Cl_2F$

First figure	= Number of C-Atoms minus 1	1
Second figure	= Number of H-Atoms plus 1	4
Third figure	= Number of F-Atoms	1

b represents the isomer 141b

Table 1 Physical and Chemical Properties of Dichlorofluoroethane

Molecular weight	117	
Physical form	liquid	
Colour	colourless	ELF ATOCHEM (1989) Internal Data
Boiling point, °C at 1013 hPa	32	Research and Consulting Company, RCC/NOTOX Proj. No 006143. The Netherlands (1989)
Freezing point, °C	-103.5	
Liquid density at 20°C, g/cm^3	1.24	Research and Consulting Company, RCC/NOTOX Proj. No 006154. The Netherlands (1989)
Vapour density at boiling point, kg/m^3	4.82	ELF ATOCHEM (1989) Internal Data
Solubility in water, g/l at 20°C	approx. 4	Research and Consulting Company, RCC/NOTOX Proj. No 006187. The Netherlands (1989)
	1-6	Different sources give varying values for the solubility in water, which mainly lie between 1 and 6 g/l
Fat solubility	completely soluble	ELF ATOCHEM (1989) Internal Data
Vapour pressure at 25°C, kPa	76.3	Research and Consulting Company, RCC/NOTOX Proj. No 006165. The Netherlands (1989)
Flammability	no flash point	Research and Consulting Company, RCC/NOTOX Proj. No 006211. The Netherlands (1989)
Octanol/water partition coefficient (Log P_{ow})	2.3	Research and Consulting Company, RCC/NOTOX Proj. No 006198. The Netherlands (1989)

2.3 ANALYTICAL METHODS

Methods for dichlorofluoroethane analysis described by Coombs *et al* (1988) are based on gas chromatography with flame ionisation detection and gas chromatography/mass spectrometry.

SECTION 3. PRODUCTION, STORAGE, TRANSPORT AND USE

There is no known natural source of dichlorofluoroethane.

3.1 MANUFACTURING PROCESS

The commercial production of dichlorofluoroethane began only a few years ago. Existing processes are based on the hydrofluorination of 1,1,1-trichloroethane or 1,1-dichloroethylene (Pittard, 1982; Walraevens *et al*, 1976).

Total current world production in 1992 was about 15 kt. Nameplate capacity of commercial units which are already in operation, or are scheduled for start-up by 1995, is over 100 kt/y. Like other hydrochlorofluorocarbons, dichlorofluoroethane is regulated under the Montreal Protocol and is thus scheduled for virtual phase-out by 2020. In view of the restrictions imposed by the Protocol, it is unlikely that production of dichlorofluoroethane will exceed 200 kt/y. This latter figure also corresponds to the maximum world market, soon after the end of the century projected by Verhille (1992).

3.2 USES

Dichlorofluoroethane is being developed as a substitute for fully halogenated chlorofluorocarbons, mainly for use as a blowing agent for polyurethane and polyisocyanurate insulating foams and as a solvent in electronic and other precision cleaning applications.

3.3 LOSS DURING DISPOSAL, TRANSPORT STORAGE AND ACCIDENTS

There is no information available on losses or accidental release.

SECTION 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION

Dichlorofluoroethane is not known to occur as a natural product. The production volume of 200 kt/y (see Section 3) will be adopted here to represent a conservative upper limit to future annual emissions, in order to assess certain aspects of the potential environmental impact of dichlorofluoroethane.

4.1 ENVIRONMENTAL DISTRIBUTION

On the basis of its physical properties dichlorofluoroethane may be expected, when released to the environment, to partition almost exclusively into the atmosphere as:

- it is a volatile liquid, with a vapour pressure at 20°C of 0.65 bar;
- its calculated Henry's Law coefficient at 20°C is about 6 g/l. bar. For an upper-limit atmospheric concentration of 100 pptv[1] (see Section 5), the equilibrium concentration in cloud and surface waters would thus be 0.6 pptw[2].

Any dichlorofluoroethane 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 days or at the very most a few weeks.

Dichlorofluoroethane present in surface or ground waters would have little tendency to partition onto biota or soil as:

- log P_{ow} is 2.3, indicating the absence of a significant potential for passive bioaccumulation;
- from various correlations, log K_{oc} may be estimated to lie in the range 1.9 - 2.2, which means that dichlorofluoroethane would be moderately mobile in soils.

[1] pptv = parts per trillion (volume);
pptw = parts per trillion (weight)

[2] The 'lifetime' is the time necessary for 63% degradation; it is equal to the 'half-life' divided by ln2 (=0.69)

4.2 ATMOSPHERIC LIFETIME

The atmospheric degradation of dichlorofluoroethane will occur mainly in the troposphere, being initiated by attack of naturally occurring hydroxyl radicals. The overall atmospheric lifetime is 10.8 years (WMO, 1991).

4.3 OZONE DEPLETING POTENTIAL

Ozone Depleting Potentials (ODPs) express the stratospheric ozone loss due to emission of a unit mass of a given compound, divided by the ozone loss due to emission of the same mass of reference compound.

Recent estimates (WMO, 1991) of the ODP of dichlorofluoroethane, carried out using 3 different atmospheric models, give results in the range 0.10-0.12, relative to a reference value of 1.0 for CFC-11. Moreover, the "semi-empirical" ODP was found to be 0.11 (WMO, 1991) and the latter value was adopted as the best estimate of the ODP for regulatory purposes in the 1992 Montreal Protocol Revision.

The ODP value may vary upwards or downwards in the future, as the models are refined and new kinetic data become available. For instance, use of a recently revised value of the rate constant for the reaction of OH radicals with CCl_3CH_3 (the reference reaction for atmospheric lifetime calculations), should lead to a downward revision of the ODP of dichlorofluoroethane by about 15%.

4.4 GLOBAL WARMING POTENTIAL

Global Warming Potentials (GWPs) express the radiative forcing (increase in earthward infra-red radiation flux) due to emission of a unit mass of a given compound, divided by the radiative forcing due to emission of the same mass of a reference compound.

Based on the lifetimes quoted above, the Halocarbon Global Warming Potential (HGWP) of dichlorofluoroethane is 0.12 (AER, 1992) relative to a reference value of 1.0 for CFC-11. This assessment assumes a pulse emission and an infinite Integration Time Horizon (ITH), which is mathematically equivalent to a steady-state calculation.

GWPs may also be expressed relative to CO_2 as the reference substance, and assessed over a finite ITH. For dichlorofluoroethane the corresponding values are 1800, 580 and 200 (relative to

reference values of 1.0 for CO_2), for ITHs of 20, 100 and 500 years respectively (WMO, 1991; IPCC, 1992).

4.5 TROPOSPHERIC OZONE FORMATION

As discussed in WMO (1989), dichlorofluoroethane is too unreactive in the atmosphere to make any significant contribution to local urban tropospheric ozone formation, and the related "photochemical smog", near the emission sources.

4.6 DEGRADATION MECHANISM AND PRODUCTS

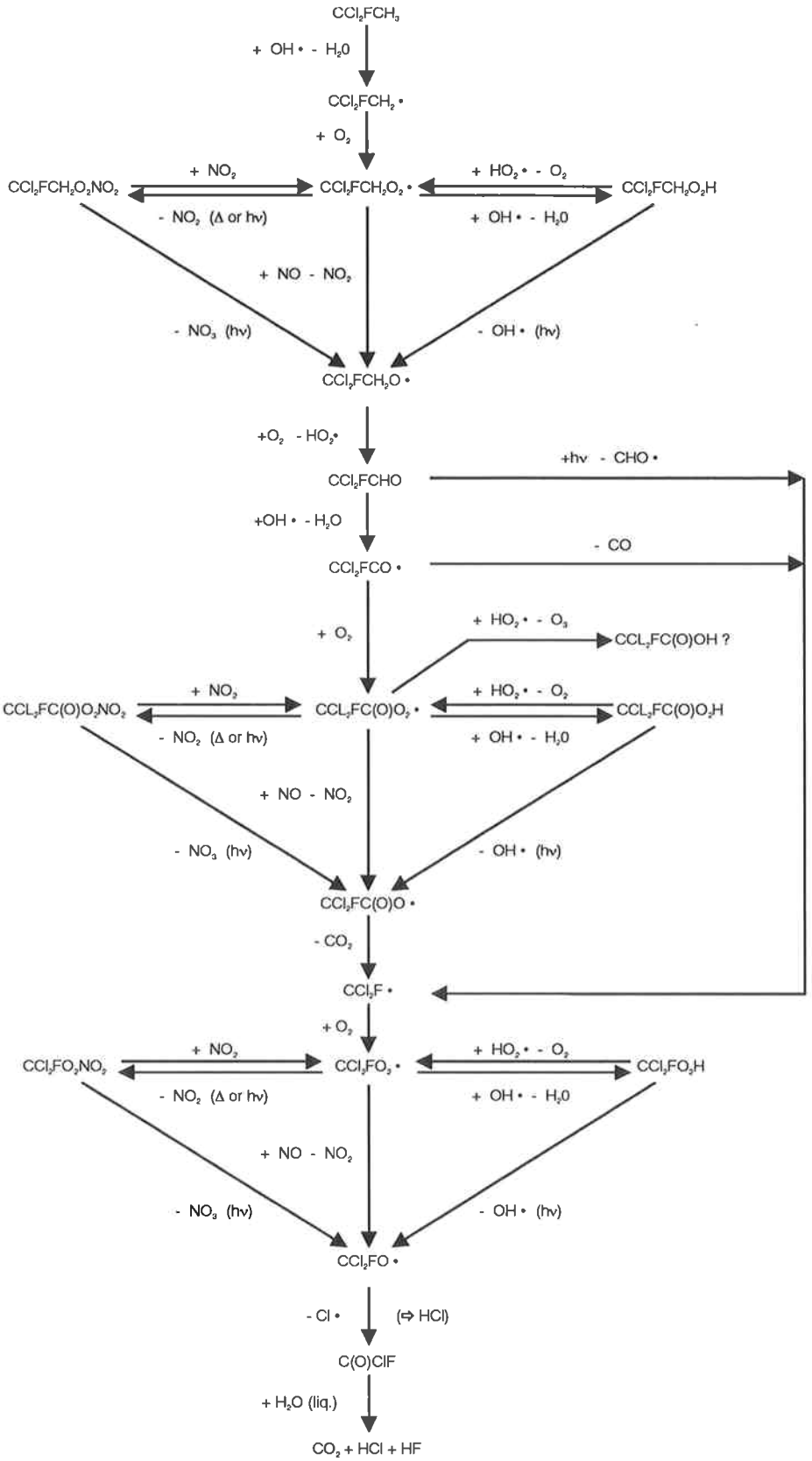
Support for the basic tropospheric degradation mechanism for dichlorofluoroethane proposed in UNEP/WMO (1989) has been provided by a number of recent laboratory studies (WMO, 1991; Edney *et al*, 1991; STEP/AFEAS, 1991; Tuazon and Atkinson, 1993; STEP/AFEAS, 1993; NASA/NOAA/AFEAS, 1993).

Breakdown of dichlorofluoroethane in the troposphere will be initiated by OH radicals and will proceed via various free-radical and molecular intermediates to give CO_2, COClF and HCl (see reaction scheme). The latter two species are expected to be removed from the atmosphere, within a few days to a few months, by uptake into clouds, rain and the oceans, COClF then being rapidly hydrolysed to the ultimate breakdown products CO_2, HCl and HF (AFEAS, 1992; STEP/AFEAS, 1993).

Although various peroxynitrates ($CCl_2FCH_2O_2FO_2NO_2$, $CCl_2FC(O)O_2NO_2$, $CCl_2FO_2NO_2$), hydroperoxides ($CCl_2FCH_2O_2H$, CCl_2FO_2H), a peroxyacid ($CCl_2FC(O)O_2H$) and an aldehyde (CCl_2FCHO) may be formed during the degradation of dichlorofluoroethane, they are not thought to play a significant role in its tropospheric chemistry, being rather short-lived intermediates.

Previous reports (STEP/AFEAS, 1991; WMO, 1991) raised the possibility of transport of chlorine to the stratosphere by the peroxynitrate $CCl_2FC(O)O_2NO_2$, on account of the long lifetime of this compound with respect to thermal decomposition in the upper troposphere. Recent modelling studies (NASA/NOAA/AFEAS, 1993) conclude that the peroxynitrate will not make any significant contribution to stratospheric chlorine, since: (a) carbon-carbon cleavage will occur to a large extent in the precursor species CCl_2FCHO and $CCl_2FC(O)$, thus by-passing the formation of the peroxynitrate and (b) whatever peroxynitrate is formed is likely to be photolysed fairly rapidly or transported to the lower troposphere where its thermal decomposition is rapid.

Figure 1 Tropospheric Degradation Mechanism For HCFC-141b



There is a possibility that minor amounts of dichlorofluoroacetic acid (CCl_2FCOOH) may be formed in the degradation of dichlorofluoroethane, by pathways discussed in WMO (1989). Experimental data are however not available to test this assumption, which is based on the existence of analogous reactions in the case of non-halogenated compounds.

4.7 CONTRIBUTION OF DEGRADATION PRODUCTS TO ENVIRONMENTAL CHLORIDE AND FLUORIDE AND TO THE ACIDITY OF RAINWATER

Assuming an atmospheric release rate of 200 kt dichlorofluoroethane per year (conservative upper limit), complete conversion of the latter into HCl (2 mol/mol dichlorofluoroethane) and HF (1 mol/mol dichlorofluoroethane) and uniform scavenging of the HCl and HF into the global average rainfall of 5×10^{11} kt/y, it follows that the levels of chloride, fluoride and acidity thus produced are low compared with those arising from existing sources:

- Cl^- production from dichlorofluoroethane would be 120 kt/y, i.e. insignificant compared with the natural atmospheric chloride flux of roughly 10^7 kt/y, mainly arising from sea-salt aerosols (WMO, 1989);

- F^- production would be 30 kt/y, i.e. very low compared with the estimated atmospheric fluoride flux of 1,000-8,000 kt/y (WMO, 1989);

- the contribution of dichlorofluoroethane to the fluoride concentration in rainwater would be 70 pptw; this should be compared with typical fluoride concentrations in "background" rainwater of around 10 ppbw, i.e. 150 times greater , and with levels of about 1 ppmw used for the fluoridation of drinking water, i.e. 15,000 times greater (WMO, 1989);

- the hydrochloric and hydrofluoric acids formed from dichlorofluoroethane and scavenged in rainwater would represent an acidity of 5×10^9 mol H^+/y, which is over 2,000 times less than the acidity arising from natural and anthropogenic emissions of SO_2 and NO_x (UKRGAR, 1990).

Thus the contribution of dichlorofluoroethane to acid rain would be negligible.

4.8 BIODEGRADATION

In the closed bottle assay with activated sludge the percentage of transformation of dichlorofluoroethane after 28 days was only 2-3 % (Oyama, 1990).

Under laboratory conditions, aerobic degradation of dichlorofluoroethane by the methane-oxidising bacterium *Methylosinus trichorsporium OB 3b* was complete within 5 hours (De Flaun *et al*, 1992).

Degradation of dichlorofluoroethane was also demonstrated with the ammonia oxidising bacterium *Nitrosomas europa*, (Hyman *et al*, 1992).

The wide dissemination and abundance of methanotrophs and ammonia oxidising bacteria in the environment suggests that these organisms may provide a natural sink.

SECTION 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Schauffler (in NASA/NOAA/AFEAS, 1993) measured troposheric levels of dichlorofluoroethane of 0.2-0.4 pptv above California in March 1992 and 0.75-1.5 pptv in the northern hemisphere in Spring 1993. The abundance was much lower in the southern hemisphere (0.25 pptv at 70°S). Monteka *et al.* (1994) reported a global-mean tropospheric concentration in mid-1993 of 0.7 pptv, with an increase of 0.9 pptv, i.e. approximately a factor of 3, during 1993.

A conservative upper limit to possible future tropospheric concentrations of dichlorofluoethane can be estimated by assuming that atmospheric emissions are as high as 200 Kt/y (see Section 3.1) and that the steady state is reached, i.e. the rate of destruction of dichlorofluoethane by reaction with hydroxyl radicals is equal to its rate of input into the atmosphere. The resulting calculated upper-limit concentration is 100 pptv.

No observations of dichlorofluoroethane in other environmental compartments have yet been reported.

Human Exposure

A Workplace Environmental Exposure Level Guide (WEEL) of 500 ppm (8 hour time weight average-TWA) has been recommended by the American Industrial Hygiene Association (AIHA, 1991). At present only limited information on human exposure to dichlorofluoroethane vapours in the working area are available. Typical values of 8 h -TWA measures for different occupations in a production plant ranged from 1 to 70 ppm (Allied Signal, 1993). Instant values measured in an Application Research Laboratory ranged from 10 to 100 ppm in the room where machines using dichlorofluoroethane as a solvent were operating; in addition 8h-TWA measures were found to be around 2 to 9 ppm for technicians working in the machine room and in a contiguous laboratory room (Elf Atochem, 1993).

SECTION 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Environmental testing of dichlorofluoroethane has only been carried out on aquatic organisms.

6.1 ALGAE

The 72 h - No Observed Effect Concentration (NOEC) for both growth rate and biomass for algae (*Selenastrum capricornutum*) was > 44 mg/l in a static test using a sealed test system (Groeneveld and Kuijpers, 1991).

6.2 INVERTEBRATE AQUATIC SPECIES

With *Daphnia magna*, the 48 h - EC_{50} was 31.2 mg/l using a sealed vessel: first effects were observed at 25 mg/l (Briand and Hervouet, 1989).

6.3 FISH

The 96 h - LC_{50} for zebra fish (*Brachidanio rerio*) was 126 mg/l in a static test using a sealed vessel (Bazzon and Hervouet, 1989).

From these experiments it can be assumed that dichlorofluoroethane has a low acute toxicity to aquatic organisms. The low octanol/water partition coefficient ($logP_{ow}$ < 3; see Table 1) makes bioaccumulation of dichlorofluoroethane unlikely.

SECTION 7. KINETICS AND METABOLISM

7.1 ANIMAL STUDIES

A low level of dechlorination (about 1%) was observed *in vitro* (Van Dyke, 1977) when rat hepatic microsomes were incubated with dichlorofluoroethane. There is no apparent defluorination of dichlorofluoroethane *in vivo* as demonstrated by the lack of urinary fluoride excretion in the sub-chronic 90 day toxicity study in Fischer 344 rats (see Section 8.2) and in the 2-year chronic toxicity study in Sprague-Dawley rats (see Section 8.3) exposed at concentrations up to 97,000 mg/m^3 (20,000 ppm).

Recently Anders (1992) has shown that pyridine-induced rat hepatic microsomes *in vitro* can transform dichlorofluoroethane into 2,2-dichloro-2-fluoroethanol. It is thought that the oxygenation of dichlorofluoroethane is essentially catalysed by cytochrome P450 2E1 as this enzymatic system is known to be induced by pyridine. The *in vitro* rate constants found for this biotransformation were: Km = 0.39 mM and Vmax = 2.08 nmol/mg protein/h. Metabolite formation was not quantifiable when normal microsomal fractions from non pyridine treated rats or rats treated with diallyl sulphide, a selective inhibitor of P450 2E1, were used (Loizou and Anders, 1993).

In an *in vivo* screening test for absorption and metabolism (Zwart, 1989) 7 groups of 5 male Sprague-Dawley rats were exposed to dichlorofluoroethane vapours by inhalation in a closed loop system to fixed initial concentrations ranging from 340 to 12,320 mg/m^3 (70 to 2,500 ppm). The exposure periods ranged from 16 to 20 hours. Expired CO_2 was absorbed with soda-lime. The concentrations in the chambers were continuously monitored by an infra-red analyser. The author stated that the sensitivity of this technique would allow the detection of metabolism of the material above 0.15%. The results suggest that absorption took place but that if any metabolism occurred it was limited and not detectable under the conditions of the screening study.

Loizou and Anders (1993) exposed male Fischer 344 rats to dichlorofluoroethane at concentrations ranging from 4,800 to 72,000 mg/m^3 (1,000 to 14,800 ppm) for 6 hours. The chamber concentrations were quantified at 10 minute intervals by gas chromatography with the flame-ionisation detection. Urine was collected during 24 hours following the end of exposure. The kinetic constants for uptake and metabolism were established. There was an initial period of rapid dichlorofluoroethane uptake that lasted about 80 minutes followed by a slow linear uptake. The initial phase was attributed to uptake and equilibration of dichlorofluoroethane, and the later phase to a saturable metabolism or deposition of the material in poorly perfused tissues. The kinetic

constants for the metabolism were: Km = 59.9 μmol/l and Vmax = 1.75 μmol/h. The high Km indicated a low affinity of dichlorofluoroethane for the metabolising enzyme. A linear relationship between dichlorofluoroethane exposure concentration and urinary 2,2-dichloro 2-fluoroethanol excretion was found.

A more sensitive procedure has been used by Harris and Anders (1991) and Loizou and Anders (1993) to investigate the *in vivo* metabolism of dichlorofluoroethane. Male Fischer 344 rats were exposed individually by inhalation in a closed-chamber system to 55,200 mg/m^3 (11,400 ppm) dichlorofluoroethane in air for 2 hours. Dichlorofluoroethane concentrations in the chamber were measured during exposure by gas chromatography coupled with mass spectroscopy (GC-MS). Immediately after cessation of exposure the animals were placed in metabolism cages and urine was collected for 15 hours. Livers of the treated rats were removed for covalent protein binding analysis in cytosolic and microsomal fractions. Covalent binding of fluorinated metabolites of dichlorofluoroethane to liver proteins was not detected by 19F NMR indicating that this compound is not metabolised to acylating intermediates. However, urine samples were found to contain a single fluorinated metabolite, which was identified as glucoronic 2,2 dichloro 2-fluoroethanol, at an average concentration of 1.0 μmol (N = 3). Free 2,2-dichloro 2-fluoroethanol and dichlorofluroacetic acid were not detectable in the urine. In an other study by the same authors dichlorofluoroacetic acid was detected in the urine of rats exposed for 4 hours to a high concentration (192,000 mg/m^3 = 40,000 ppm) of dichlorofluoroethane indicating that oxidation of 2,2-dichloro-2-fluoroethanol may occur at concentration higher than 55,200 mg/m^3 (11,400 ppm).

Overall dichlorofluoroethane appears to be easily and quickly absorbed via the respiratory route and undergoes a saturable uptake in the rat. Dichlorofluoroethane can be metabolised to 2,2-dichloro 2-fluoroethanol by cytochrome P450 2E1 but is a poor substrate to the metabolising enzyme. This metabolite is excreted in the urine in the form of its glucuronide conjugate. The level of metabolisation of dichlorofluoroethane observed in the rat is low.

7.2 HUMAN

No data exist for absorption, distribution, metabolic transformation or elimination of dichlorofluoroethane in man.

SECTION 8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO SYSTEM

8.1 SINGLE EXPOSURES

No mortality was observed in rats receiving acute oral doses of 5,000 mg/kg dichlorofluoroethane (Sarver, 1988; Liggett *et al*, 1989) or dermal doses of 2,000 mg/kg in rats (Gardner, 1988; Janssen and Pot, 1988) and rabbits (Brock, 1988a). No signs of toxicity were seen other than piloerection with oral dosing (Liggett *et al*, 1989). Acute inhalation studies in mice demonstrated a 30 min LC_{50} of 485,000 mg/m^3 (100,000 ppm) (Davies *et al*, 1976). The 4 h LC_{50} in rats was 300,700 mg/m^3 (62,000 ppm) (Hardy *et al*, 1989a). Sixty percent of the mice exposed to 388,000 mg/m^3 (80,000 ppm) died within 30 minutes (Vlachos, 1989).

Pre-narcotic signs were observed in rats (Hardy *et al*, 1989a) and mice (Vlachos, 1989) during inhalation exposure at levels higher than 145,500 mg/m^3 (30,000 ppm).

Narcosis was induced in mice by the following exposure conditions: 388,000 mg/m^3 for 15 minutes; 310,400 mg/m^3 (64,000 ppm) for 30 minutes and 198,850 mg/m^3 (41,000 ppm) for 6 hours (Davies *et al*, 1976; Vlachos, 1989).

8.2 REPEATED EXPOSURE

No adverse clinical signs and only slight biochemical changes (no details given) were observed in rats (number and strains unspecified) exposed for 6 h/d, 5 d/wk for 2 weeks to 48,500 mg/m^3 (10,000 ppm) dichlorofluoroethane by inhalation (Pennwalt, 1987).

An inhalation study in rats and guinea pigs (number and strains unspecified) exposed 2h/d, 6d/wk for 4 weeks, to levels of 40,000 to 50,000 mg/m^3 (8,240 to 10,300 ppm) of dichlorofluoroethane demonstrated a reduction of bodyweight gain, minor changes in biochemical parameters (slight decrease of haemoglobin and moderate leukocytosis) and some unspecified minor changes in the liver and kidney function, and histopathological effects in the respiratory tract. In this study, the purity of the substance and specific isomer used were not stated (Nikitenko and Tolgskaja, 1965).

In a 2 week inhalation study 5 groups 10 m and 10 f Sprague-Dawley rats were exposed 6h/d for 9 days to 0 or 24,250 to 97,000 mg/m^3 (5,000 to 20,000 ppm) dichlorofluoroethane. Pre-narcotic signs were seen during exposure to concentrations of 41,225 mg/m^3 (8,500 ppm) and higher.

These signs were accompanied at 97,000 mg/m^3 (20,000 ppm) by a decreased body weight gain in males and a slightly reduced food intake in both sexes. The following plasma constituents were increased at the levels indicated: glucose and AST (97,000 mg/m^3 = 20,000 ppm), proteins, cholesterol and sodium (70,328 mg/m^3 = 14,500 ppm), phosphate (41,225 mg/m^3 = 8,500 ppm) and calcium (24,250 mg/m^3 = 5,000 ppm) (Coombs *et al*, 1988).

In a 13 week inhalation study (in which some animals were killed after 4 weeks), 4 groups each of 15m and 15f Fischer 344 rats were exposed 6h/d, 5d/wk to 0, 9,700, 38,800 or 97,000 mg/m^3 (2,000, 8,000 or 20,000 ppm) dichlorofluoroethane. Alertness was reduced at 97,000 mg/m^3 (20,000 ppm) (Yano *et al*, 1989, Landry *et al* 1989). The bodyweight and food consumption were slightly reduced in all exposed groups. However, the temperature in the exposure chambers was unintentionally raised during the first period of the study and it is assumed that reduced bodyweight and food consumptions were caused by this, except perhaps for the animals exposed to the higher concentration level. After both 4 and 13 weeks of exposure plasma cholesterol, triglyceride, and glucose were slightly raised in the rats exposed to 97,000 mg/m^3 (20,000 ppm). There were no changes in haematological or histopathological findings which could be attributed to exposure to dichlorofluoroethane.

More recently a 28-day inhalation toxicity study followed by a 14 day recovery period was conducted in the rat (Hino *et al*, 1992). Five males and 5 females per group were exposed to 0, 7,275, 38,800 or 97,000 mg/m^3 (0, 1,500, 8,000 or 20,000 ppm respectively) over 6h/d and 5d/wk. The only treatment related effects were a small bodyweight gain decrease and a higher serum cholesterol level in males of the 20,000 ppm group. This result is consistent with the NOEL of 8,000 ppm described above in the Yano *et al* (1989) study.

Based on these data the no effect level of dichlorofluoroethane is 38,400 mg/m^3 (7,900 ppm).

8.3 LONG-TERM EXPOSURE

A combined chronic toxicity/carcinogenicity study in rats with exposure levels of vapours of dichlorofluoroethane ranging from 7,275 to 97,000 mg/m^3 (1,500 to 20,000 ppm) was recently reported by Millischer *et al* (1994). Description of the study and detailed results are given in Section 8.8.

8.4 SKIN AND EYE IRRITATION, SENSITISATION

8.4.1 Skin irritation

Two studies were conducted on groups of 6 New-Zealand albino rabbits (Brock, 1988b; Ligett, 1988a). Application of 0.5 ml of the undiluted material to the intact skin under occlusive patch for 4 or 24 hours did not induce signs of dermal irritation during the 3 day observation period.

8.4.2 Eye irritation

Two studies were conducted on groups of 6 New-Zealand albino rabbits (Brock, 1988c; Ligett, 1988b). The undiluted material (0.1 ml) was instilled into the eyes. No signs of irritation occurred within the 3 days in one study but Brock (1988c) described dichlorofluoroethane as a mild irritant to the eye. The majority of rabbits in this study showed conjunctival redness, mild chemosis and blood-tinged discharge.

8.4.3 Skin sensitisation

The Magnusson-Kligman maximisation test was conducted on Hartley Dunkin guinea-pigs using the protocol specified in OECD Guideline 406 (Kynoch and Parcell, 1989). No delayed contact hypersensitivity was found in any of the 20 guinea pigs exposed to dichlorofluoroethane.

8.5 SPECIAL STUDIES

8.5.1 Respiratory Function

Three groups of 3 male Wistar rats were exposed to 48,500 mg/m^3 (10,000 ppm) dichlorofluoroethane for 25 minutes. No effect on respiratory frequency was observed, although there was a small change in respiratory amplitude suggesting decrease of tidal volume. It was concluded that dichlorofluoroethane is not irritant to the respiratory tract (Janssen, 1989). Repeat exposure inhalation studies have not shown morphological change in the lung. (See Section 8.2).

8.5.2 Cardiovascular Function

In an experimental screening study (Mullin, 1977) in conscious dogs, inhalation exposure to high concentrations of dichlorofluoroethane for 5 minutes, followed an intravenous epinephrine challenge (8 μ/Kg), induced cardiac sensitisation at concentrations of 24,250 mg/m^3 (5,000 ppm) and above. The no-effect level for cardiac sensitisation in this study was 12,125 mg/m^3 (2,500 ppm). In a later

study (Hardy *et al,* 1989b) in both dogs and cynomologous monkeys, using a protocol similar to the preceding study, cardiac sensitisation was induced with a epinephrine challenge following exposure concentrations between 24,250 mg/m^3 and 48,5000 mg/m^3 (10,000 ppm) in both species. In both of the preceding studies, the potency of dichlorofluoroethane to induce cardiac sensitisation was comparable to that of CFC-11.

8.5.3 Neurotoxicity

The potential neurotoxic effects of dichlorofluoroethane were investigated in a 16-week inhalation neurotoxicity study on the rat (Coombs *et al,* 1992). Groups of 10 males and 10 female Sprague Dawley rats were exposed (whole body) 6h/d, 5d/wk for 16 weeks, to vapour of dichlorofluoroethane at concentrations of 0, 7,275, 24,250 and 72,750 mg/m^3 (0, 1,500, 5,000 and 15,000 ppm) in air. On the day after the cessation of exposure and 2 and 4 weeks post-exposure, neurobehavioral functions were assessed using the Irwin neurobehavioral screen methodology (Irwin, 1968) as indicated by WHO (1986) which includes observations in home cage, on the bench, in the hand and in a few selected situations including testing for grip strength, pain response, corneal and pinna reflexes and catalepsy. Whole-body perfusion fixation was performed on 5 males and 5 females of each group at week 17 and 21. The brain was weighed and the following nervous tissues after haematoxylin-eosin staining were examined histopathologically by light microscopy: medulla/pons, cerebellar cortex, cerebral cortex, sciatic nerve, spinal cord (3 levels), tibial nerve, dorsal and ventral root fibres (C3-C6, L1-L4). There were no treatment related effects at any of the three test concentrations of dichlorofluoroethane on neurobehavioral observations, on the brain weight or on any of the series of nervous tissues examined microscopically. This result is consistent with the lack of any clinical signs in the sub-acute and subchronic studies (see Section 8.2) as well as in the 2-year chronic toxicity study (see Section 8.3) in rats exposed to concentrations up to 97,000 mg/m^3 (20,000 ppm).

8.6 REPRODUCTIVE EFFECTS, EMBRYOTOXICITY AND TERATOLOGY

8.6.1 Reproductive Effects

A two-generation reproduction, inhalation study with vapours of dichlorofluoroethane was recently reported by Rusch *et al* (1994). Four groups of 32 male and 32 female Sprague Dawley rats were exposed (whole body) to levels of dichlorofluoroethane in air of 0, 9,700, 38,800 or 97,000 mg/m^3 (0, 2,000, 8,000 or 20,000 ppm) 6 h/d, 7 d/wk. This group represented the F_0 generation. They were exposed continuously for 10 weeks starting from 7 weeks of age. At that point they were

paired for the first of two matings. Exposures were continued through until day 4 postpartum of the second litter (F_{1b}).

Starting at four weeks of age, selected offspring (28 males and 28 females) from the first litter (F_{1a}) were exposed to dichlorofluoroethane at the same exposure levels as their parents. These groups were exposed 6 h/d, 7 d/wk for 16 weeks and then paired. As with the F_0 animals, exposures of F_1 parents were continued through to the end of lactation of the F_2 generation.

The only reproductive effect associated with the exposures was a possible decrease in the number of litters from the F_0 parents in the 97,000 mg/m^3 (20,000 ppm) exposure level group. The percent of females with litters was 91 %, 88 %, 72 % for the 9,700, 38,800 and 97,000 mg/m^3 (2,000, 8,000 or 20,000 ppm) group respectively, and 94 % for the control. Following weaning of the pups, all animals in the F_0 generation groups were remated with different partners of the same exposure group. The percent of females with litters this time was again higher in the control, low and mid-level exposure groups than in the high level exposure group (88 %, 89 %, 90 % and 64 % respectively). Only eight females failed to deliver litters at both mating intervals, these were distributed 1, 2, 1 and 4 in the control, low, mid and high level exposure groups respectively. Histological examination of reproductive organs of these eight animals did not reveal any consistent pattern suggesting a treatment related effect. This effect on litter size was not seen when the F_1 parents were mated to produce the F_2 pups. In the F_1 generation, 82 %, 86%, 93 % and 82% of the females in the 0, 9,700, 38,800 and 97,000 mg/m^3 (0, 2,000, 8,000 and 20,000 ppm) exposure level groups, respectively, produced viable litters.

Litter size was comparable for all groups at the first F_0 mating. At the second F_0 mating, the number of pups per litter was lower in the 97,000 mg/m^3 (20,000 ppm) exposure level group (12.1) compared to the controls (14.8). With the F_1 mating, the litter size in the high level exposure group was smaller (11.6) than the controls (13.4).

At day 4 all litters were culled randomly to eight pups, where possible four males and four females. Survival and individual pup weights were similar through this interval for all litters. The F_{1b} pups were killed at day 4. The body weights for the pups in the F_{1a} litters were generally similar. From day 14 on, pup weight in all three exposure groups were lower than in the controls, but there was no dose relationship. Body weights for the F_2 pups were comparable across groups from birth through day 7. From day 14 through day 21 (termination) the pup weights in the high level exposure group were lower than corresponding controls. There was no effect on pup viability, either to day 4 or to weaning. The ratio of male to female pups was generally similar throughout the study. There was a delay in males in the 97,000 mg/m^3 (20,000 ppm) exposure group (50.8 d)

showing balanopreputial skin fold cleavage, a measure of male sexual maturation, compared to the controls (48.7 d). This difference was however not statistically significant and was very likely to be related to the lower body weights in the treated group. Females did not show any intergroup differences in the number of days to vaginal opening.

In the adult animals, body weights tended to be lower in the 97,000 mg/m^3 (20,000 ppm) exposure group and occasionally in the 38,800 mg/m^3 (8,000 ppm) exposure level group compared to controls. Food consumption, while variable did not show a pattern suggestive of a treatment related effect. Water consumption was higher in the 97,000 mg/m^3 (20,000 ppm) exposure level group. Histopathological examination of reproductive organs did not show evidence for treatment related effects.

In summary, exposure of rats to dichlorofluoroethane at a level of 97,000 mg/m^3 (20,000 ppm) was associated with a decrease in the litters in the F_1 but not in the F_2 generation, a decrease in the number of pups per litter at the F_{1b} and F_2 matings but not at the F_{1a} mating. At birth, pup weights tended to be similar, but by day 14, pups in the high exposure group tended to have lower body weights than controls. This lower body weight may have retarded the sexual maturation of the males but not the females. There were no effects on viability or sexual distribution in litters. For reproductive effects, 38,800 mg/m^3 (8,000 ppm) appeared to represent a no-observed-effect level. The no-observed effect for non-reproductive effects was 97,000 mg/m^3 (20,000 ppm).

8.6.2 Embryotoxic and Teratogenic Effects

Four groups of 25 pregnant female Sprague-Dawley rats were exposed to 0, 15,520, 38,800 or 97,000 mg/m^3 (0, 3,200, 8,000, 20,000 ppm) of dichlorofluoroethane for 6 h/d from days 6 to 15 of pregnancy (Rusch *et al*, 1994). Some clinical signs of maternal toxicity (pre-narcotic signs, pilo-erection and reduced alertness) were observed at all concentrations. At the highest concentration, salivation, hunched posture and diaphragmatic breathing, a marked increase in water consumption, a transient reduction in food intake and a marginal reduction of bodyweight gain were observed. In the 97,000 mg/m^3 (20,000 ppm) exposed group, the incidence of early and late embryonic death was significantly increased. Reduced litter and mean foetal weights and retarded ossification were observed. There was no evidence of maternal or embryotoxic effects at 38,800 mg/m^3 (8,000 ppm). There was no evidence of teratogenicity at any level tested.

Four groups of 16 pregnant female New-Zealand white rabbits were exposed to 0, 6,790, 20,370 or 61,110 mg/m^3 (0, 1,400, 4,200 or 12,600 ppm) of dichlorofluoroethane for 6 h/d from day 7 to day 19 of pregnancy (Rusch *et al*, 1994). Signs of maternal toxicity including pre-narcotic signs,

palpebral ptosis, respiratory disturbances and body-weight loss were observed in the 20,370 and 61,110 mg/m^3 (4,200 and 12,600 ppm) exposed groups. There was no indication of any treatment related effects on embryo or foetal development or any evidence of teratogenicity at any exposure level. Exposures at 6,790 mg/m^3 (1,400 ppm) represented a no-adverse-effect level.

8.7 MUTAGENICITY

The mutagenic properties of dichlorofluoroethane were investigated in bacterial assays, chromosomal aberration assays on mammalian cell cultures *in vitro* and *in vivo* micronucleus assays.

The results are reported in Table 2.

When dichlorofluoroethane (purity > 99.5%) was tested in the Ames assay, with a vapour phase exposure, a negative response in both *Salmonella typhimurium* and *Escherichia coli* was obtained (May, 1989). A recent Ames test conducted with dichlorofluoroethane samples of current industrial production gave also negative response (May, 1991).

Earlier studies using less pure dichlorofluoroethane gave negative response in one study (Koorn, 1988) and weak positive response in two other studies with *Salmonella* TA 1535 in the absence of metabolic activation using a high vapour concentration exposure (DuPont, 1978; Hodson-Walker and May, 1988a). The occasional positive responses in the Ames test are possibly linked with some unidentified impurities which were present in the earlier laboratory sample materials and which are no longer present in the current industrial dichlorofluoroethane material.

A DNA-repair test conducted in *Escherichia coli*, in liquid phase, gave negative results (Hodson-Walker and May, 1988b). Furthermore, the HGPRT-assay in Chinese hamster V79 cells gave negative response with dichlorofluoroethane in the vapour phase (Bootman *et al*, 1988a).

Overall, it is concluded from the tests for gene mutation and the DNA-repair test, that dichlorodifluoroethane in itself does not have genotoxic potential.

Four *in vitro* and two *in vivo* clastogenicity assays were conducted. A small increase in chromosome aberrations was observed *in vitro* in Chinese hamster ovary (CHO) cells exposed to dichlorofluoroethane in the vapour phase (Bootman and Hodson-Walker, 1988; Hodson-Walker, 1990a). The effect was present only at high concentrations and was not influenced by the presence of S9-metabolic activation. When the same type of cells were exposed to liquid

Table 2 The genetic toxicology of dichlofluoroethane in *in vitro* and *in vivo* studies

Assay	Strain/type	Test conditions	Results	Sample purity (%)	References
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537, TA 1538	± S-9; vapour phase tested	TA 1535 weakly positive with and without S-9	< 99.5	DuPont, 1978
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537, TA 1538	± S-9; vapour phase tested up to 30%	TA 1535 positive with and without S-9 at 10-20 % conc.	99.6	Hodson-Walker and May, 1988a
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537, TA 1538	± S-9; vapour phase tested up to 30%	negative	99.95	May, 1989*
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537, TA 1538	± S-9; vapour phase tested up to 42%	negative	97.6	Koorn, 1988
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537, TA 1538	± S-9; vapour phase tested up to 30 %	negative;	99.8	May, 1991
Escherichia Coli (Ames test)	WP 2 uvr A tryptophan dependent	± S-9; vapour phase tested up to 30 %	negative	99.95	May, 1989*
HGPRT Test Chinese Hamster cells	V 79 cell	± S-9; vapour phase tested up to 35 %	negative	99.6	Bootman *et al*, 1988a
*Escherichia coli*DNA Repair	WP2, WP67, CMB71	± S-9; liquid phase tested up to 10 mg/ml	negative	99.6	Hodson-Walker and May, 1988b
Chromosomal aberration	C.H.O.	± S-9; liquid phase tested up to 13.2 mg/ml	gaps increased with S-9 at 1-3 mg/ml	99.5	Wilmer and De Vogel, 1988
Chromosomal aberration	C.H.O.	± S-9; Vapour phase tested up to 35%	positive with and without S-9	99.6	Bootman and Hodson-Walker, 1988
Chromosomal aberration	C.H.O.	± S-9, vapour phase tested up to 10%	positive with and without S-9	99.83	Hodson-Walker, 1990a*
Lymphocyte cytogenetic	Human lymphocytes	± S-9, vapour phase tested up to 35% (1988)	negative	99.83	Hodson-Walker, 1990b*
Bone-marrow Micronucleus	Mice (CDI)	*in vivo* testing (2,000 - 8,000 20,000 ppm/6 h)	negative	99.6	Bootman *et al*, 1988b
Bone-marrow Micronucleus	Mice (CDI)	*in vivo* testing (2,600 - 10,000 34,000 ppm/6 h)	negative	99.98	Vlachos, 1989*

* PAFT 1989-1994

dichlorofluoroethane only an increase of gaps in the presence of S9 was found (Wilmer and De Vogel, 1988). In addition, a human lymphocyte cytogenetic assay also gave negative responses to dichlorofluroethane in the vapour phase (Hodson-Walker, 1990b).

Two micronucleus tests were performed in male and female mice. Both gave negative results after a 6 hour nose-only inhalation at concentrations, ranging from 9,700 to 97,000 mg/m^3 (2,000 to 20,000 ppm) (Bootman *et al*, 1988b) or a 6 hour whole-body exposure at concentrations ranging from 17,460 (3,600 ppm) to 164,900 mg/m^3 (33,400 ppm) (Vlachos, 1989). These tests were conducted at sub-lethal concentrations high enough to induce over toxicity signs in the mice exposed to the highest concentrations (nervous system depressing effects). There was no indication of toxicity to bone marrow as the PCE: PCN ratios were not modified. It is considered likely that dichlorofluoroethane would reach the bone marrow because it is a small C_2 molecule which can easily diffuse in the organs as this is demonstrated for instance by its anesthetic encephalic barrier.

The tests performed for clastogenicity suggest dichlorofluoroethane may have weak *in vitro* clastogenic activity on CHO cells. The inconsistency between the findings in tests using vapour and liquid exposures to hamster cells and human cells make the interpretation difficult. The lack of effect of dichlorofluoroethane in the micronucleus assay in mice suggests that the weak *in vitro* clastogenic action apparent in CHO cells, if real, would not be expressed *in vivo*.

Based on the overall weight of evidence it is concluded that dichlorofluoroethane does not demonstrate toxicologically significant genotoxic activity.

8.8 CARCINOGENICITY

The results of a combined chronic toxicity/carcinogenicity study were reported by Millischer *et al* (1994). Four groups of Sprague Dawley rats containing 80 males and 80 females were exposed (whole body) 6 h/d, 5d/wk for 104 weeks to dichlorofluoroethane. The exposure levels were 0 (controls), 7,275, 24,250 and 72,750 mg/m^3 (0, 1,500, 5,000 and 15,000 ppm). The high exposure level was increased to 97,000 mg/m^3 (20,000 ppm) after 17 weeks of exposure in the light of the minimal toxicity noted to this point. The chamber concentrations were monitored by gas chromatography at regular intervals during the 6 hours exposure. Investigations included body weight, food consumption, mortality, clinical signs, haematology, blood and urine biochemistry and organ/tissue macroscopic and histological examinations. After 52 weeks of exposure, 10 animals of each group were killed to provide interim haematological, biochemical and histopathological information.

The survival rate in the exposed groups did not differ from the control groups and no clinical signs could be associated with exposure to dichlorofluoroethane. There was a slight but statistically significant reduction in body weight gain and food consumption in the high dose group, particularly in the males. There were no inter-group differences in the incidence of ocular abnormalities or in any of the haematological parameters. There were no blood and urinary biochemical effects although occasional increases in serum triglycerides in high dose group rats may have been related with the treatment. There was no increase in urinary fluoride excretion. There were no organ weight effects due to dichlorofluoroethane. There were no intergroup differences in respect of macroscopic and microscopic examinations at 52 weeks. After 104 weeks there were increased incidences of testicular masses in the highest exposure group. Histological examinations did not show any treatment related lesions in any organs and tissues of the female. In the males there were no treatment related effects except the following findings: a) small increase in the number of vacuolated sinusoidal histiocytes of the cervical lymph nodes in the high concentration group; b) statistically significant increase of the incidence of hyperplasia and benign tumours of the testicular interstitial cells (Leydig cells) in the medium and high concentration groups and c) non-statistically significant increase in atrophy of seminiferous tubules in the high concentration group.

There was no dose-response relationship for the increased incidence of the Leydig cell benign tumours as the incidence at 97,000 mg/m^3 (20,000 ppm) was lower than the incidence at 24,250mg/m^3 (5,000 ppm) (4.3% ; 5.7 % ; 20 % ; 17.1 % respectively for control, low, medium and high exposure concentration level). These incidences were outside of the historical control range of the Sprague-Dawley strain found in the testing laboratory (0 to 10 %). The tumours were found predominantly in rats killed at termination.

The no-observed adverse effect level in the study was 7,275 mg/m^3.

Discussion

The 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 form a few percent in Sprague Dawley up to 100% in some Wistar derived and in Fisher 344 rats (Bär, 1992). These tumours do not usually progress to malignancy in the rat as this is indicated by the absence or extremely rare occurrence of malignant Leydig cell tumours (e.g. none found in several thousands of control Fisher rats) (Boorman *et al*, 1990; Iawata *et al*, 1991). They appear late in life and are not life-threatening to the rats. They are associated with the ageing process. Leydig cells secrete sex hormones (e.g. testosterone, dihydroandrosterone, oestradiol).

The high incidence of hyperplasia and tumours of these testicular cells in old rats is thought to be related to senile endocrine disturbances (Mostofi and Price, 1973).

Various conditions have been shown to increase Leydig cell hyperplasia or tumour incidence in the rat, including senility *per se*, and oestrogenic treatments (Mostofi and Bresler, 1976). In addition, an increased incidence of Leydig cell tumours has been described with a large number of substances covering a wide variety of chemical structures e.g. isradipine (Roberts *et al*, 1989), mesulargine (Prentice *at al,* 1992), cimetidine (Leslie *et al,* 1981), hydralazine, carbamazepine (Griffith R W, 1988) and even such a common dietary component as lactose (Bär, 1992).

Dichlorofluoroethane (as well as the substances mentioned above), does not demonstrate significant mutagenic activity (see Section 8.7). This leads to the conclusion that the increased incidence of Leydig cell tumours observed in the long-term rat study with dichlorofluoroethane is very likely attributable to a non-genotoxic mechanism. Non-genotoxic mechanisms have been frequently associated with hormonal imbalance, especially an imbalance of sex hormones (Neuman, 1991). Indirect evidence of hormonal disturbance with dichlorofluoroethane in male rats is provided by the finding of increased atrophy of seminiferous testicular tubules in the high concentration group.

Findings of the 2-year inhalation study with dichlorofluoroethane indicate that all Leydig cell hyperplasia and tumours occurred late in the life of the rats and were not associated with increased mortality. Thus the basic characteristics of the spontaneous appearance of this type of neoplasm in the rat were not changed by dichlorofluoroethane, suggesting that the chemical simply tends to exaggerate the hormonal disturbances linked with senility.

Moreover, in contrast to the rat, the Leydig cell tumour occurrence in man is extremely low, representing less than 3% of all testicular neoplasms (Mostofi and Price, 1973). The rarity of Leydig cell tumours in the human being as compared to the high spontaneous incidence in the rat make the relevance of the rat findings to man highly questionable.

Consequently the increased frequency of the benign Leydig cell tumours observed in rats exposed to dichlorofluoroethane at the high concentrations of 24,250 and 97,000 mg/m^3 (5,000 and 20,000 ppm) is considered not to indicate a tumourigenic risk to man at the recommended exposure levels.

SECTION 9. EFFECTS ON MAN

There are no reported adverse health effects which can be ascribed to dichlorofluoroethane.

The American Industrial Hygiene Association's Workplace Environmental Exposure Level (WEEL) Committee assigned dichlorofluoroethane an occupational exposure limit (8-hour time weighted average) of 500 ppm (2,425mg/m^3) (AIHA, 1991).

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Responsible Editor: D. A. Stringer, ECETOC
Av. E. Van Nieuwenhuyse, 4 (Bte 6)
B - 1160 Brussels, Belgium
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