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No 25

1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) CAS No. 2837-89-0

July 1994

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ECETOC

Joint Assessment of Commodity Chemicals No. 25

1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124)

CAS No. 2837-89-0

July 1994

European Centre for Ecotoxicology and Toxicology of Chemicals

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Joint Assessment of Commodity Chemicals No. 25

1-Chloro-1,2,2,2-

tetrafluoroethane (HCFC 124)

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ECETOC Jacc Report No. 25

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 review 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. 12 originally published in May 1990 on 1-chloro-1,2,2,2-tetrafluoroethane (HCFC 124; CAS No. 2837-89-0). The text revisions introduce new environmental and toxicology data.

1-Chloro-1,2,2,2-tetrafluoroethane (HCFC-124)

CONTENTS

SECTION 1. SUMMARY AND CONCLUSIONS

1-Chloro-1,2,2,2-tetrafluoroethane (chlorotetrafluoroethane), a non-flammable colourless gas at room temperature, is currently under development as a chlorofluorocarbon alternative and is not yet available in commercial quantities.

The atmospheric degradation of chlorotetrafluoroethane will occur mainly in the troposphere by reaction with naturally occurring hydroxyl radicals. Its overall atmospheric lifetime is approximately 6.9 years and about 95% of the degradation will occur in the troposphere. Chlorotetrafluoroethane has a low calculated ozone depletion potential (ODP) of 0.022 and a global warming potential of 0.10 relative to a reference value for both indices of 1.0 for trichlorofluoromethane (CFC-11).

In limited studies in rats to evaluate metabolic fate and pharmacokinetics, chlorotetrafluoroethane appears to undergo oxidative metabolism resulting in the excretion of trifluoroacetic acid and fluoride ion in the urine. Studies to assess the metabolic fate of inhaled tetrafluoroethane in rats, mice, and hamsters are currently in progress.

Chlorotetrafluoroethane has a low order of acute inhalation toxicity with a 4-hour LC_{50} in rats between 1,283,400 and 1,674,000 mg/m^3 (230,000 and 300,000 ppm). The main toxicological action of this fluorocarbon during exposure is weak anaesthesia. As with many other halocarbons and hydrocarbons, inhalation of high concentrations of chlorotetrafluoroethane, followed by an intravenous epinephrine challenge to simulate stress, can induce a cardiac sensitization response in dogs. In these experimental screening studies, cardiac sensitisation (life-threatening arrhythmia) was seen at concentrations of 146,000 mg/m^3 (26,000 ppm) and above. The no-observable-effect-level was 55,800 mg/m^3 (10,000 ppm).

In a 2-week inhalation toxicity study, rats exposed to 558,000 mg/m^3 (100,000 ppm) chlorotetrafluoroethane showed no adverse effects. In 90-day studies at concentrations as high as 279,000 mg/m^3 (50,000 ppm), rats and mice showed minimal toxic effects such as slight central nervous system depression and minor blood chemistry changes. No-observable-effect level in these 90-day studies was 27,900 mg/m^3 (5,000 ppm) for male rats whilst for male mice a NOEL was not achievable. For female rats and mice a NOEL of 15,000 ppm was established. A lifetime inhalation toxicity/carcinogenicity study in rats is currently in progress.

No evidence of embryotoxicity or teratogenicity of chlorotetrafluoroethane was seen in developmental studies by inhalation in rats and rabbits at exposure levels as high as

279,000 mg/m^3 (50,000 ppm). Minimal evidence of maternal toxicity was seen at concentrations of 83,700 mg/m^3 (15,000 ppm) and above in each of these studies.

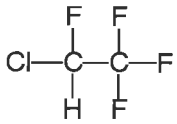
Chlorotetrafluoroethane was not mutagenic either in *in vitro* or in *in vivo* studies using bacteria or yeast or mammalian cell lines or the mouse micronucleus assay.

There are no reported effects of chlorotetrafluoroethane in man. An occupational exposure limit (8-hour average) of 1,000 ppm (5,580 mg/m^3) is recommended by AIHA.

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

2.1 IDENTITY

Chemical Structure:



Chemical Formula: $CHClF\text{-}CF_3$

Common Name: 1-Chloro-1,2,2,2-tetrafluoroethane
Chlorotetrafluoroethane

IUPAC Name: Ethane, 2-chloro-1,1,1,2-tetrafluroro-

Common Synonyms: 1,1,1,2-Tetrafluoro-2-chloroethane
Fluorocarbon 124
HFA-124; HCFC-124[1]

CAS Registry Number: 2837-89-0

EINECS Number: 220-629-6

Conversion Factors: 1 ppm = 5.58 mg/m^3 at 25°C
1 mg/m^3 = 0.179 ppm at 25°C

2.2 PHYSICAL AND CHEMICAL PROPERTIES

Chlorotetrafluoroethane is a nonflammable colourless gas. Some physical and chemical data are given in Table 1.

1 Abbreviations mean: Hydro-Chloro-Fluoro-Carbon C_2HCF_4

First figure = number of C-Atoms minus 1	1
Second figure = number of H-Atoms minus 2	2
Third figure = number of F-Atoms	4
	= HCFC 124

2.3 ANALYTICAL METHODS

A method of analysis for chlorotetrafluoroethane has been described using gas chromatography with dual flame ionization detection (Malley, 1991a).

Table I Physical and chemical properties of chlorotetrafluoroethane*

Molecular Weight	136.5
Physical form	Gas
Colour	Colourless
Boiling point, °C at 1013 hPa	-12
Liquid density at 25°C, g/ml	1.36
Vapour density (air = 1)	4.7
Vapour pressure, hPa at 25°C	3,850
% Volatiles by volume at 20°C	100
Solubility in water at 25°C, g/l at 1013 hPa	1.45
Solubility in organic solvents	Miscible with acetone, ethanol, petroleum solvents
Log P_{ow}	1.9-2.0
Log K_{oc}	1.7-1.9 (calculated)
Flammability	Nonflammable

* From E. I. duPont de Nemours & Company, Inc.; Material Safety Data Sheet - HCFC124; January 1993.

SECTION 3. PRODUCTION, STORAGE, TRANSPORT AND USE

Processes for the production of chlorotetrafluoroethane are still under development. Possible routes are hydrofluorination of tetrachloroethylene or hydrodechlorination of 1,1-dichloro-1,2,2,2 tetrafluoroethane (CFC-114a). The grade of purity obtained is greater than 99%.

So far, chlorotetrafluoroethane is produced only on a small scale. Like other hydrochloro-fluorocarbons, chlorotetrafluoroethane is regulated under the Montreal Protocol and is thus scheduled for virtual phase-out by 2020. Chlorotetrafluoroethane is being developed as a substitute for fully halogenated chlorofluorocarbons. Its main potential applications are believed to be as a component for refrigerant blends and as a blowing agent for polystyrene and polyolefin foams.

SECTION 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION, AND IMPACT

4.1 SOURCE

There is no known natural source of chlorotetrafluoroethane.

The figure of 25 kt/y is adopted here to represent a conservative upper limit to possible future annual emissions, in order to assess certain aspects of the potential environmental impact of chlorotetrafluoroethane.

4.2 ENVIRONMENTAL DISTRIBUTION

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

- it is a gas at room temperature and atmospheric pressure, boiling at -12°C;
- its Henry's Law constant for dissolution in water is 1.45 g/l.bar at 25°C; for an atmospheric concentration of 7 ppt (v/v) (i.e., the calculated steady-state concentration resulting from emissions of 25 kt/y), the equilibrium concentration in cloud and surface waters would thus be 0.01 ppt (w/w);
- any chlorotetrafluoroethane 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 volatilization of days or a few weeks at the very most.

Moreover, any chlorotetrafluoroethane present in surface or ground waters would have little tendency to partition onto biota or soil. Log P_{ow} is 1.9-2.0, indicating a low potential for passive bioaccumulation. From various correlations, logK_{oc} is estimated to lie in the range 1.7-1.9, which means that chlorotetrafluoroethane would be moderately mobile in soils. The atmospheric lifetime of chlorotetrafluoroethane (about 7 y, see below) is much longer than either the intrahemispheric or interhemispheric mixing times. Therefore this compound will become more or less uniformly distributed in the atmosphere on a global scale (at a concentration <7 ppt (v/v), see above).

4.3 ATMOSPHERIC LIFETIME[1]

The atmospheric degradation of chlorotetrafluoroethane will occur mainly (about 95%) in the troposphere, being initiated by attack of naturally occurring hydroxyl radicals. The lifetime with respect to this process is estimated to be 7.3 y. Additionally some chlorotetrafluoroethane will be transported to the stratosphere and be degraded there by reaction with hydroxyl radicals, oxygen atoms and by photolysis. The overall atmospheric lifetime is estimated to be 6.9 years (WMO, 1991).

4.4 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 a reference compound.

The latest estimates of the ODP of chlorotetrafluoroethane, carried out using 3 different atmospheric models, give results in the range 0.016-0.034 relative to a reference value of 1.0 for CFC-11. The "semi-empirical" ODP was found to be 0.022 (WMO, 1991). 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 chlorotetrafluoroethane by about 15%.

4.5 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 chlorotetrafluoroethane is 0.10 (AER, 1992) relative to a reference value of 1.0 for

1 Lifetime (LT) is the time necessary for 63% degradation; it is equal to the "half-life" divided by ln2 (=0.69)

trichlorofluoromethane (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 chlorotetrafluoroethane, the corresponding values are 1,500; 440 and 150 (relative to a reference value of 1.0 for CO_2 at each ITH), for ITHs of 20, 100, and 500 y respectively (WMO, 1991; IPCC, 1992).

4.6 TROPOSPHERIC OZONE FORMATION

Chlorotetrafluoroethane 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 (WMO, 1989).

4.7 DEGRADATION MECHANISM AND PRODUCTS

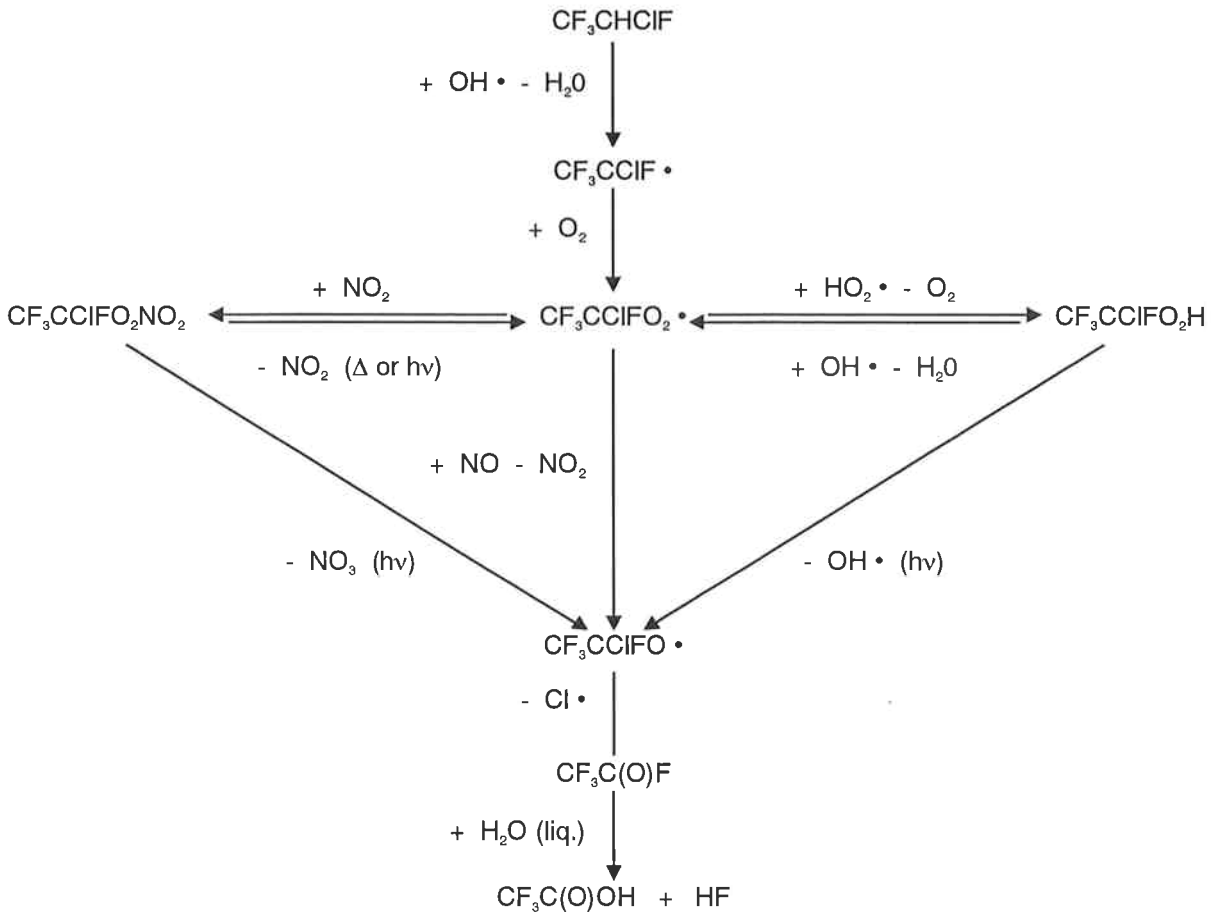
(see Figure 1 for reaction scheme)

Support for the basic tropospheric degradation mechanism for chlorotetrafluoroethane proposed in WMO (1989) has been provided by recent laboratory studies (see, for example: WMO, 1991; Edney and Driscoll, 1992; Tuazon and Atkinson, 1993).

Breakdown of chlorotetrafluoroethane in the troposphere will be initiated by OH-radicals and will proceed via various free-radical intermediates to give HCl and CF_3COF. The latter are expected to be removed from the atmosphere within a few days to a few months, by uptake into clouds, rain and the oceans, CF_3COF then being rapidly hydrolysed to trifluoroacetic acid (TFA) and hydrofluoric acid (HF) (AFEAS, 1992; STEP/AFEAS, 1993; Franklin, 1993).

Although a peroxynitrate ($CF_3CClFO_2NO_2$) and a hydroperoxide (CF_3CClFO_2H) may be formed during the degradation of chlorotetrafluoroethane, they are not thought to play a significant role in the atmospheric chemistry of chlorotetrafluoroethane and are probably rather short-lived intermediates.

Figure 1 Tropospheric Degradation Mechanism for HCFC-124



4.8 CONTRIBUTION OF DEGRADATION PRODUCTS TO ENVIRONMENTAL CHLORIDE, FLUORIDE AND TRIFLUOROACETATE AND TO THE ACIDITY OF RAINWATER

Assuming an atmospheric release rate of 25 kt chlorotetrafluoroethane/y (likely upper limit), complete conversion of the latter into HCl, HF, and CF_3COOH (1 mol of each per mol chlorotetrafluoroethane) and uniform scavenging of the acids produced into the global average rainfall of 5×10^{11} kt/y, it follows that the levels of chloride, fluoride, and acidity produced are low compared with those arising from existing sources for the following reasons:

- Cl^- production from chlorotetrafluoroethane would be 7 kt/y, i.e. insignificant compared with the natural atmospheric chloride flux of roughly 1×10^7 kt/y, mainly arising from sea-salt aerosols (WMO, 1989);

- F^- production would be 4 kt/y, i.e. very small compared with the estimated atmospheric fluoride flux of 1,000-8,000 kt/y (WMO, 1989);

- the contribution of chlorotetrafluoroethane to the fluoride concentration in rainwater would be 7 ppt (w/w); this should be compared with typical fluoride concentrations in "background" rainwater of around 10 ppb (w/w), i.e. 1,500 times greater, and with levels of about 1 ppm (w/w), used for the fluoridation of drinking water, i.e. 150,000 times greater (WMO, 1989);

- the contribution of chlorotetrafluoroethane to trifluoroacetate in rainwater would be about 40 ppt (w/w);

- the hydrochloric, hydrofluoric, and trifluoroacetic acids formed from chlorotetrafluoroethane and scavenged in rainwater would represent an acidity of a little over 5×10^8 mol H^+/y, i.e. 20,000 times less than the acidity arising from natural and anthropogenic emissions of SO_2 and NO_x (UKRGAR, 1990). Thus the contribution of chlorotetrafluoroethane to acid rain would be negligible.

4.9 BIODEGRADATION

In a closed-bottle assay for ready biodegradability, chlorotetrafluoroethane in aqueous solution appeared to be stable (1-2% loss) over a 4 wk period (Tobeta, 1992).

SECTION 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

No observations of chlorotetrafluoroethane in the atmosphere or other environmental compartments have yet been reported.

SECTION 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

No data are available on the effects of chlorotetrafluoroethane on environmental organisms.

SECTION 7. KINETICS AND METABOLISM

7.1 ANIMAL STUDIES

Limited metabolic data have been published on chlorotetrafluoroethane. Olson *et al* (1991) exposed rats to 558,000 mg/m^3 (10,000 ppm) chlorotetrafluoroethane for two hours and found both inorganic fluoride and trifluoroacetic acid in their urine, both being products of an oxidative metabolism. Increases in urinary fluoride levels in rats exposed by subchronic inhalation to chlorotetrafluoroethane had also been reported earlier by Brewer (1977a) and Malley (1991a). Additional evidence for an oxidative metabolism was provided by Harris *et al* (1992) who exposed rats for 6 hours to 558,000 mg/m^3 (10,000 ppm) chlorotetrafluoroethane and found trifluoroacetylated proteins in liver and trifluoroacetic acid in urine, similar to earlier results reported by Harris *et al* (1991). The oxidative metabolism was approximately 5 fold less for chlorotetrafluoroethane compared to halothane (1-chloro-1-bromo-2,2,2-trifluoroethane) and dichlorofluoroethane. Work is currently underway (Anders, 1993a,b) to investigate the metabolism of inhaled chlorotetrafluoroethane in rats, mice, and hamsters.

7.2 HUMAN STUDIES

No data were found for humans relative to the absorption, distribution, metabolic transformation or elimination of chlorotetrafluoroethane.

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

8.1 SINGLE EXPOSURE

In recent studies by Kelly (1990) groups of 6 male rats were exposed, nose-only, for single 4-h periods to atmospheres containing chlorotetrafluoroethane vapour at concentrations of 267,840, 902,800, 1,283,400, or 1,674,000 mg/m^3 (48,000, 162,000, 230,000 or 300,000 ppm). Aside from a slight weight loss one day post-exposure, rats exposed at the lowest exposure level showed no clinical signs of toxicity during or after exposure. At concentrations of 902,800 and 1,283,400 mg/m^3 (162,000 and 230,000 ppm), no mortality occurred but rats did show a temporary weight loss, decreased acoustic-startle responses, prostration, lethargy and incoordination; these anaesthetic effects disappeared shortly after exposure. At 1,674,000 mg/m^3 (300,000 ppm), the same clinical signs occurred, but 6 of 6 rats died during the 4-h exposure. Under the conditions of this study, the 4-h LC_{50} of chlorotetrafluoroethane in rats was estimated to be between 1,283,000 and 1,674,000 mg/m^3 (230,000 and 300,000 ppm). Wada (1977) had previously reported a 10-min approximate lethal concentration of 2,460,000 mg/m^3 (440,000 ppm) for mice; exposure at 2,230,000 mg/m^3 (400,000 ppm) for 10 min produced no mortality. Anaesthesia was observed at 837,000 mg/m^3 (150,000 ppm) and no effects were seen at 558,000 mg/m^3 (100,000 ppm).

In an earlier study by Coate (1976), a single 6-h exposure to chlorotetrafluoroethane at a concentration of 2,010,000 mg/m^3 (360,000 ppm) was not lethal to rats but rapidly depressed motor activity; this was followed by anaesthesia after one hour. Rats exposed to 558,000 mg/m^3 (100,000 ppm) were active for 30 min but then inactive until termination of exposure. Rats exposed to 2,010,000 mg/m^3 (360,000 ppm) gained less weight than either the controls or the lower exposure group between days 1 and 8.

When dogs were exposed to chlorotetrafluoroethane for 10 min at exposure concentrations ranging from 2,232,000 to 3,906,000 mg/m^3 (400,000 to 700,000 ppm), light surgical anaesthesia was rapidly induced. Complete recovery occurred within 7-10 minutes post-exposure (Van Poznak and Artusio, 1960).

8.2 REPEATED EXPOSURE

Trochimowicz *et al* (1977) had reported no adverse effects in 10 rats exposed by inhalation to chlorotetrafluoroethane for 6 h/d, 5 d/wk for 2 wk at a concentration of 558,000 mg/m^3

(100,000 ppm). A four-week inhalation study was conducted by Malley (1990) with five groups of 10 male and 10 CD®BR female rats. The exposure regimen was 6 h/d, 5 d/wk for 4 wk at concentrations of 0, 2,790, 11,160, 55,800 or 279,000 mg/m^3 (0, 500, 2,000, 10,000 or 50,000 ppm) chlorotetrafluoroethane. Compound related effects on body weight, food consumption, mortality, clinical laboratory parameters, organ weights, and tissue morphology did not occur at any exposure concentration. During the exposure period, rats exposed to 279,000 mg/m^3 (50,000 ppm) appeared to be lethargic and uncoordinated. However, at the end of the daily exposure period, when the animals were removed from the chambers, no evidence of lethargy or incoordination was observed. The no-observable-effect level (NOEL) was considered to be 55,800 mg/m^3 (10,000 ppm).

In a 90-day inhalation toxicity study by Malley (1991a), 20 CD®BR rats/sex/level were exposed to chlorotetrafluoroethane for 6 h/d, 5 d/wk at concentrations of 0, 27,900, 83,700, or 279,000 mg/m^3 (0, 500, 15,000 or 50,000 ppm). Ten rats/sex/level were designated for a neurotoxicity evaluation using a Functional Observational Battery (FOB) and for an additional one-month recovery period. There were no compound-related effects on body weight, food consumption, mortality, clinical signs, haematology, organ weights, and tissue morphology at any exposure concentration. During exposure, rats exposed to 279,000 mg/m^3 (50,000 ppm) were less responsive to stimuli compared to control rats as demonstrated by a decreased reaction to a knock on the exposure chamber wall. In addition, on the day following the last exposure, male rats exposed to 83,700 or 279,000 mg/m^3 (15,000 or 50,000 ppm) chlorotetrafluoroethane had decreased arousal times (in 4 of 10 and 6 of 10 rats, respectively). Relative to blood chemistry measurements, at the 45-day clinical evaluation interval, male rats exposed to 83,700 and 279,000 mg/m^3 (15,000 or 50,000 ppm) had lower serum triglyceride concentrations than controls and female rats at 279,000 mg/m^3 (50,000 ppm) showed increased alkaline phosphatase activity. At all exposure levels, fluoride concentration in blood and urine was elevated at several sampling intervals during exposure and also at one month post-exposure. Male rats exposed at the two highest exposure levels also showed a mild diuresis, probably a result of increased osmotic activity from the excreted fluoride ion rather than a direct effect of the compound. The no-observable-effect level (NOEL) for this 90-day study was considered to be 27,900 mg/m^3 (5,000 ppm) for male rats and 83,700 mg/m^3 (15,000 ppm) for female rats.

Malley (1991b) also conducted a 90-day inhalation toxicity study in 20 CD®-1(ICR)BR mice/sex/group exposed for 6 h/d, 5 d/wk at the same concentration levels of chlorotetrafluoroethane as used in the rat study (see above). Responses in mice were similar to the responses described for rats. There were no compound-related effects on mortality, food consumption, clinical signs, haematology, organ weights and tissue morphology at any exposure concentration for either male or female mice. In male mice killed at 90-days, body weights were 6

to 7% lower than controls (not dose related) and hepatic ß-oxidation activity was approximately two-fold higher at all exposure levels, while serum triglyceride concentrations were decreased at the two highest exposure levels. During exposure, both male and female mice exposed at 279,000 mg/m^3 (50,000 ppm) chlorotetrafluoroethane were less responsive to stimuli (knocking on chamber window) compared to controls. All the effects seen in female or in male mice during exposure disappeared after 30 days post-exposure. Although all these effects in male mice were slight and of negligible toxicological significance, a NOEL was not achieved for male mice. For female mice, the NOEL was 83,700 mg/m^3 (15,000 ppm).

One 90-day inhalation study in rats using a sample of unknown purity had been conducted by Brewer (1977a) at exposure levels up to 27,900 mg/m^3 (5,000 ppm) chlorotetrafluoroethane and was reported earlier by ECETOC (1990). However, it will not be discussed here since the recent studies in rodents (Malley, 1991a,b) at similar and higher exposure levels, and conducted for even longer durations, have not confirmed the findings reported by Brewer (1977a).

The minimal, reversible effects seen in the preceding studies are not considered to be adverse. Therefore the subchronic no-observable-adverse-effect level (NOAEL) of chlorotetrafluoroethane for rats or mice is considered to be 279,000 mg/m^3 (50,000 ppm).

8.3 LONG-TERM EXPOSURE

No data available.

A lifetime inhalation toxicity/carcinogenicity bioassay in rats under the sponsorship of the Program for Alternative Fluorocarbon Toxicity Testing (PAFT) is currently in progress. Approximately 85 rats/sex/group are being exposed to chlorotetrafluoroethane for 6 h/d, 5 d/wk for 104 wk at concentrations of 0, 27,900, 83,700 or 279,000 mg/m^3 (0, 5,000, 15,000 or 50,000 ppm). The exposure phase of this study began in October 1992 and no results are available at the present time.

8.4 SKIN AND EYE IRRITATION/ALLERGIC SENSITIZATION

As chlorotetrafluoroethane is a gas at ambient temperature, studies to assess skin and eye irritation as well as skin sensitization have not been carried out. No evidence of skin or mucosal irritation was seen in rats exposed by inhalation on an acute or a repeated basis (see section 8.2).

8.5 SPECIAL STUDIES: CARDIOVASCULAR AND RESPIRATORY EFFECTS

In an experimental screening study (Mullin, 1976) in dogs, inhalation exposure to high concentrations of chlorotetrafluoroethane for 5 minutes, followed by an intravenous epinephrine challenge (~8 μg/kg) induced cardiac sensitization at concentrations of 146,000 mg/m^3 (26,000 ppm) and above. The NOEL cardiac sensitization in this study was 55,800 mg/m^3 (10,000 ppm).

In repeated exposure studies (see Section 8.2) by the inhalation route, chlorotetrafluoroethane concentrations as high as 279,000 to 558,000 mg/m^3 (50,000 to 100,000 ppm) produced no clinical or histopathological evidence of respiratory irritation in mice or rats respectively.

Older studies to evaluate anaesthetic potency of chlorotetrafluoroethane have been reported earlier (ECETOC, 1990).

8.6 DEVELOPMENTAL TOXICITY/REPRODUCTIVE PERFORMANCE

In a developmental toxicity study by Alvarez (1990), 24 pregnant CD®BR rats/group were exposed by whole-body inhalation to chlorotetrafluoroethane for 6 h/d on days 6 through 15 of gestation at concentrations of 0, 27,900, 83,700 or 279,000 mg/m^3 (0, 5,000, 15,000 or 50,000 ppm). No evidence of embryotoxicity, foetotoxicity, or teratogenicity was seen at any exposure level. Maternal toxicity was demonstrated at 279,000 mg/m^3 (50,000 ppm) by a decreased rate of weight gain and food consumption during the first 4 days of exposure and by a reduced response to auditory stimuli during exposure but not shortly thereafter. Under these study conditions, the NOAEL for chlorotetrafluoroethane was 83,700 mg/m^3 (15,000 ppm) for the dam and 279,000 mg/m^3 (50,000 ppm) for the conceptus.

Using the same target exposure levels as the preceding study, Schroeder (1991) exposed 20 pregnant New-Zealand white rabbits/group by whole-body inhalation to chlorotetrafluoroethane vapour for 6 h/d on days 6 through 18 of gestation. There was no evidence of embryotoxicity, foetotoxicity, or teratogenicity at any exposure level. Similar to the preceding results in rats, slight maternal effects were seen at 279,000 mg/m^3 (50,000 ppm) as evidenced by decreased food consumption and decreased in-chamber activity. The no-observable-effect level (NOEL) for maternal effects was reported as 83,700 mg/m^3 (15,000 ppm) while the NOEL for developmental toxicity was considered to be 279,000 mg/m^3 (50,000 ppm).

In a limited developmental toxicity study using a sample of unknown purity, Brewer (1977b) exposed 20 pregnant Albino rats to 27,900 mg/m^3 (50,000 ppm) chlorotetrafluoroethane for 6 h/d on days 6

through 15 of gestation. No evidence of maternal toxicity, foetotoxicity, embryotoxicity, or teratogenicity was seen at this single exposure level. This study was reported in more detail earlier (ECETOC, 1990).

No data were available to evaluate the reproductive performance of male and female animals exposed to chlorotetrafluoroethane. However, in rats and mice exposed for 90 days by inhalation to chlorotetrafluoroethane concentrations as high as 279,000 mg/m^3 (50,000 ppm) (Malley, 1991a,b), no histopathological effects were seen in the reproductive organs/tract of male or female animals.

8.7 MUTAGENICITY

The *in vitro* mutagenicity potential of chlorotetrafluoroethane has been evaluated in several bacteria and cells. In a series of plate and suspension assays using *Salmonella typhimurium* (Brusick, 1976; Barsky, 1976; Longstaff *et al*, 1984; Reynolds, 1990; May, 1991), strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to various concentrations of chlorotetrafluoroethane in the presence and absence of an S-9 metabolic activation system. None of these studies showed any evidence of mutagenicity potential. Chlorotetrafluoroethane also showed no mutagenicity potential in other *in vitro* assay with *Escherichia coli* (May, 1991) and *Saccharomyces cerevisiae* (Brusick, 1976). Furthermore chlorotetrafluoroethane showed no evidence of clastogenic activity in cultured Chinese Hamster Ovary (CHO-K1) cells (Edwards, 1991) or in human lymphocytes with or without S-9 metabolic activation (Bentley, 1990).

In one *in vivo* mutagenicity study (Rickard, 1990), chlorotetrafluoroethane was tested for its ability to induce micronuclei in bone marrow polychromatic erythrocytes of male and female mice. The animals were exposed, head-only, to either 0 or 552,400 mg/m^3 (0 or 99,000 ppm) vapour in air for 6 h/day on two consecutive days. Bone marrow smears were prepared 24 and 48 h after exposure. Chlorotetrafluoroethane did not induce micronuclei and was considered negative for *in vivo* mutagenicity potential.

In conclusion, chlorotetrafluoroethane is not mutagenic *in vitro* and *in vivo.*

8.8 CARCINOGENICITY

No data to evaluate the carcinogenicity potential of chlorotetrafluoroethane were available. However, an inhalation carcinogenicity bioassay in rats by the inhalation route is currently underway (Section 8.3).

SECTION 9. EFFECTS ON HUMANS

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

The American Industrial Hygiene Association's Workplace Environmental Exposure Level (WEEL) Committee assigned chlorotetrafluoroethane an occupational exposure limit (8-hour time-weighed average) of 1,000 ppm (5,580 mg/m^3) (AIHA, 1992).

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