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Concise International Chemical Assessment Document 11

1,1,1,2-Tetrafluoroethane

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170¹ for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

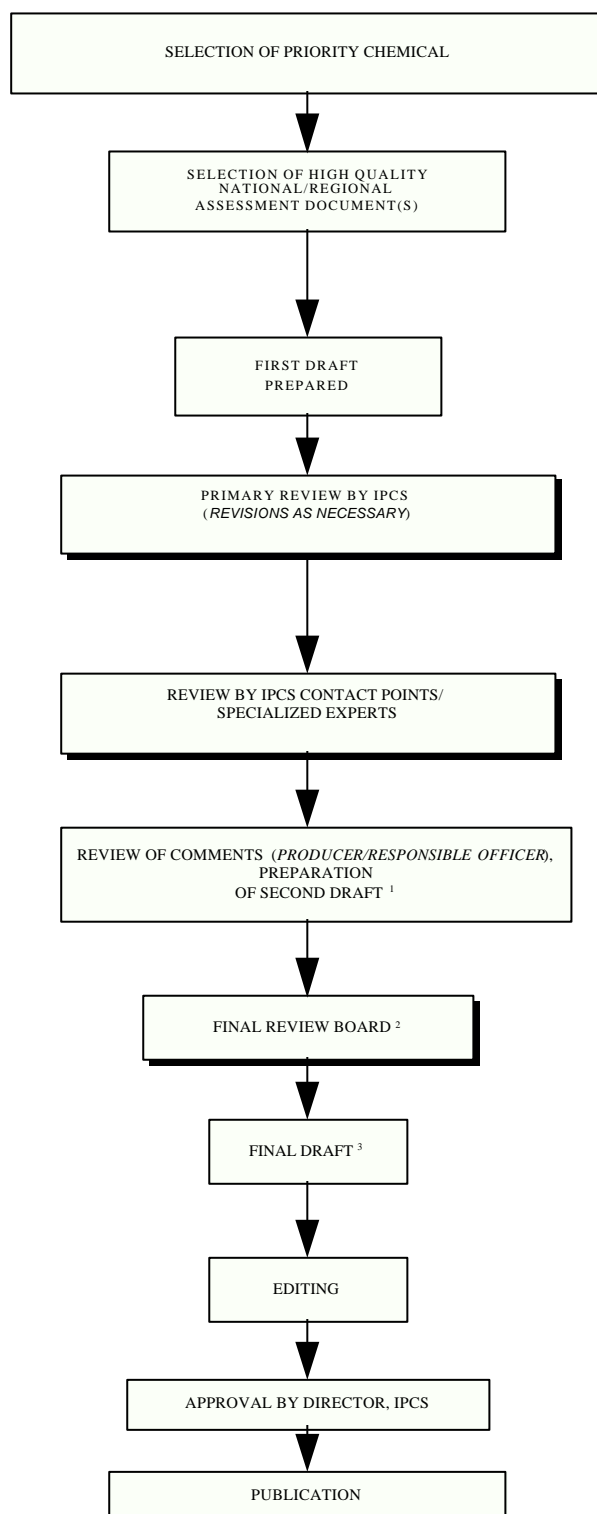
The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



¹ Taking into account the comments from reviewers.

² The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.

³ Includes any revisions requested by the Final Review Board.

experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on 1,1,1,2-tetrafluoroethane was based on a review of human health concerns (primarily occupational) prepared by the United Kingdom Health and Safety Executive in 1995 (Strandring et al., 1995). Additional information on effects on human health and the environment was identified in ECETOC (1995). Data identified up to December 1994 were covered by these reviews. Additional data identified after these reviews were published have been incorporated as appropriate. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Berlin, Germany, on 26–28 November 1997. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 1281) for 1,1,1,2-tetrafluoroethane, produced by the International Programme on Chemical Safety (IPCS, 1998), has also been reproduced in this document.

1,1,1,2-Tetrafluoroethane (CAS no. 811-97-2) is a gaseous fluorocarbon that is manufactured by the reaction of hydrogen fluoride with trichloroethylene in a closed system. It is used primarily as a refrigerant for “high-temperature” refrigeration, such as domestic refrigerators and automobile air conditioners. Other potential uses include application in plastic foam blowing, as a solvent for special cleaning applications, as an aerosol propellant for medical inhalers, and as a fire extinguishant in place of halons.

Little information was identified on exposure of the general public or workers to 1,1,1,2-tetrafluoroethane. During its manufacture in the United Kingdom, employee exposure to the chemical was very low, with no measured concentrations above 7 ppm (29.2 mg/m³). There are no exposure measurements from its use in the manufacturing industry and no data on the exposure of field servicing personnel. The situation in the workplace in the United Kingdom and analogous data from a single study of exposure to dichlorotrifluoroethane (HCFC 123) would suggest that exposure to 1,1,1,2-tetrafluoroethane in the workplace is normally low (i.e., below 10 ppm [41.7 mg/m³]), with occasional short-term peak exposures of up to several hundred parts per million.

Information on the effects of 1,1,1,2-tetrafluoroethane on humans is limited to one report; most available data on the toxicological effects of 1,1,1,2-tetrafluoroethane have been derived from studies conducted with laboratory animals. 1,1,1,2-Tetrafluoroethane exhibits relatively low toxicity. A reduction in maternal

body weight gain in rabbits exposed to 40 000 ppm (166 800 mg/m³) 1,1,1,2-tetrafluoroethane and signs of delayed fetal development in rats following exposure of the dams to 50 000 ppm (208 500 mg/m³) 1,1,1,2-tetrafluoroethane have been noted in developmental toxicity studies. In other toxicological investigations, adverse health effects have not been observed following exposure to concentrations up to 10 000 ppm (41 700 mg/m³). The weight of evidence for carcinogenicity is limited to an increased incidence of Leydig cell adenomas following exposure to 50 000 ppm (208 500 mg/m³), and 1,1,1,2-tetrafluoroethane has not been found to be genotoxic in studies conducted to date.

The low toxicity of 1,1,1,2-tetrafluoroethane to the few aquatic organisms tested as well as its high volatility indicate negligible risk to aquatic organisms.

Atmospheric effects have been assessed by modelling. Recent observations have shown a rapid increase in atmospheric concentrations of 1,1,1,2-tetrafluoroethane, mainly as a result of emissions over the past decade. Modelling indicates insignificant ozone depletion potential, a significant global warming potential, and negligible acidification potential.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

1,1,1,2-Tetrafluoroethane (CAS no. 811-97-2; C₂H₂F₄; 1,2,2,2-tetrafluoroethane, HFC 134a, HFA 134a, HCFC 134a) is a gaseous fluorocarbon with a faint ether-like odour. It is soluble in alcohols, esters, and chlorinated solvents, but it is only slightly soluble in water. It has a boiling point of -26°C and a vapour pressure of 630 kPa at 25°C. Additional properties are presented in the International Chemical Safety Card reproduced in this document. The conversion for 1,1,1,2-tetrafluoroethane is 1 ppm = 4.17 mg/m³ (at 25°C). The structural formula for 1,1,1,2-tetrafluoroethane is:



3. ANALYTICAL METHODS

An unpublished method based on a Health and Safety Executive (1995) procedure has been used to monitor exposure to 1,1,1,2-tetrafluoroethane. The sample is collected diffusively onto Sphero carb and analysed by thermal desorption into a gas chromatograph fitted with a flame ionization detector (FID). The diffusive uptake rate is reported as 1.2 ng/ppm per minute, and the method has been validated down to 0.1 ppm for exposure periods of 30–480 min.¹ Pumped sampling onto Anasorb CMS followed by solvent desorption and analysis with a gas chromatograph fitted with an FID has also been validated (Griffiths, 1998). Both the Miran infrared monitor (Quantitech Ltd)² and the Innova 1312 photoacoustic monitor (CBISS)³ can be used to measure airborne concentrations of 1,1,1,2-tetrafluoroethane to sub-ppm concentrations.

There are no published methods for the biological monitoring of occupational exposure to 1,1,1,2-tetrafluoroethane. However, by analogy with other haloalkanes, it may be possible to develop biological monitoring methods based on the analysis of 1,1,1,2-tetrafluoroethane in the breathing zone or urine (Woollen et al., 1990, 1992). In addition, a study of its use in medical inhalers revealed that 1,1,1,2-tetrafluoroethane can be measured in blood samples; sampling at 2 min indicated 1,1,1,2-tetrafluoroethane levels of 200–700 ng/ml, with a substantial reduction by 12 min (Donnell et al., 1995).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

1,1,1,2-Tetrafluoroethane is manufactured by the reaction of hydrogen fluoride with trichloroethylene in a closed system. It is available as a liquefied gas and is supplied in a variety of pressurized containers. 1,1,1,2-Tetrafluoroethane is used primarily as a refrigerant for “high-temperature” refrigeration, such as domestic refrigerators and automobile air conditioners. Other potential uses include application in plastic foam blowing, as a solvent for special cleaning applications,

as an aerosol propellant for medical inhalers, and as a fire extinguishant in place of halons.

Between 1990 and 1995, the estimated global production of 1,1,1,2-tetrafluoroethane for dispersive use increased from 0.2 to 73.8 kilotonnes per year; over this same period, the estimated global release of this chemical increased from 0.1 to 20.3 kilotonnes per year (AFEAS, 1996).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

1,1,1,2-Tetrafluoroethane is expected to partition almost exclusively to the atmosphere. Aqueous discharges would be expected to volatilize, with half-lives of days to a few weeks. It is not expected that 1,1,1,2-tetrafluoroethane will accumulate in biota ($\log K_{ow} = 1.06$) or adsorb to soil or sediment ($\log K_{oc} = 1.5$). The atmospheric equilibrium concentration in cloud water has been estimated at less than 0.2 ppt by weight based on predicted atmospheric concentrations of 100–200 ppt by volume ($0.4\text{--}0.8\text{ g/m}^3$) for the year 2020 (McCulloch, 1993). The long atmospheric half-life will result in more or less uniform distribution in the atmosphere on a global scale (Franklin, 1993).

The overall estimated lifetime of 1,1,1,2-tetrafluoroethane in the troposphere is 14.6 years (IPCC, 1995); degradation is initiated by hydroxyl (OH) radicals. It is theoretically possible that 1,1,1,2-tetrafluoroethane could contribute to ozone depletion by means of CF_3O_x radicals arising from the atmospheric degradation of tetrafluoroethane; however, this contribution has been estimated to be insignificant in recent studies (Ko et al., 1994; Ravishankara et al., 1994).

1,1,1,2-Tetrafluoroethane’s global warming potential over a 100-year time horizon (relative to carbon dioxide) has been estimated at 1300, compared with 3800 for CFC-11 and 8100 for CFC-12, for which 1,1,1,2-tetrafluoroethane is the main substitute (IPCC, 1995). Franklin (1993) has estimated that 1,1,1,2-tetrafluoroethane will reach an atmospheric background concentration of 100 ppt by volume (0.4 g/m^3) by 2010–2020 and will then be responsible for only about 0.3% of the radiative forcing due to all anthropogenic greenhouse gases present in the atmosphere.

Hydroxyl radicals break down 1,1,1,2-tetrafluoroethane to form the CF_3CHFO radical, which reacts with oxygen to generate trifluoroacetyl fluoride (CF_3COF) or undergoes cleavage to give formyl fluoride (HCOF) and the CF_3 radical, which is ultimately converted to carbonyl

¹ Personal communication, ICI Laboratories, The Heath, Runcorn, UK.

² Unit 3, Old Wolverton Road, Old Wolverton, Milton Keynes, UK MK12 5NP.

³ 5-11 Coronation Drive, Bromborough, Wirral, UK L62 3LF.

fluoride (COF_2) and hydrogen fluoride (HF). Modelling studies predict that 40% of 1,1,1,2-tetrafluoroethane breakdown will proceed via the former route and 60% by the latter route (Franklin, 1993). Recent research suggests that the yield of trifluoroacetyl fluoride is in the range of 7–20% rather than 40%, as was previously assumed (Wallington et al., 1996).

The principal fate of the acid fluorides (CF_3COF , HCOF , and COF_2) will be uptake by cloud water and hydrolysis to trifluoroacetic acid, formic acid, carbon dioxide, and hydrogen fluoride. Dry deposition to ocean or land surfaces may occur to a limited extent and will be followed by hydrolysis (AFEAS, 1992, 1993).

The contribution of degradation products to environmental fluorides and acidity of rainwater is expected to be negligible (WMO, 1989; Franklin, 1993).

There are no known natural sources of trifluoroacetic acid. However, recent work (Frank et al., 1996) has measured trifluoroacetic acid in rainwater and surface waters in Europe and Israel at levels too high to be explained by the atmospheric degradation of 1,1,1,2-tetrafluoroethane and other chlorofluorocarbon substitutes. The origin of this trifluoroacetic acid is currently unexplained, and a natural source cannot be ruled out. Using the same assumptions for emission and atmospheric degradation as above (Franklin, 1993), deposition of trifluoroacetic acid in rainwater would be 45 kilotonnes per year (in the years 2010–2020), with an average concentration in precipitation globally at 0.1 g/litre. Trifluoroacetic acid will partition into the aqueous environment; assuming accumulation in the upper levels of seawater, an increased concentration of 1.5 ng/litre would be expected for each 100 kilotonnes of 1,1,1,2-tetrafluoroethane degraded.

Laboratory tests have demonstrated no appreciable degradation of 1,1,1,2-tetrafluoroethane in activated sludge (Tobeta, 1989) or by the methanotropic bacterium *Methylosinus trichosporium* (DeFlaun et al., 1992). Trifluoroacetic acid can be degraded under anoxic conditions to trifluoromethane, inorganic fluoride, methane, and carbon dioxide (Visscher et al., 1994).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

In 1995, the average atmospheric concentration of 1,1,1,2-tetrafluoroethane was about 2 ppt (8.3 ng/m^3); there had been a significant increase in concentration measured throughout 1994 and 1995, rising from about

0.3 ppt (1.3 ng/m^3) in early 1994 to a range of 1.2–3.4 ppt ($5.0\text{--}14.2 \text{ ng/m}^3$) in late 1995 (Montzka et al., 1996). Measurements were taken on land in Canada, the continental United States, Hawaii, American Samoa, and Tasmania and at sea in the Pacific and Atlantic oceans.

6.2 Human exposure

Information on potential exposure of the general public to 1,1,1,2-tetrafluoroethane was not identified, and there are limited data concerning occupational exposure. During its manufacture in the United Kingdom in a modern plant, employee exposure was very low, with no measured concentrations above 7 ppm (29.2 mg/m^3) (Strandring et al., 1995). There are no exposure measurements from its use in the manufacturing industry and no data on the exposure of field servicing personnel. At the time of review, there was only one manufacturer in the United Kingdom, although other production facilities are envisaged to come on stream in the near future. The situation in the United Kingdom and analogous data from a single study of exposure to dichlorotrifluoroethane (HCFC 123) (Strandring et al., 1995) would suggest that exposure is normally low (i.e., below 10 ppm [41.7 mg/m^3], 12-hour time-weighted average), with occasional short-term peak exposures of up to several hundred parts per million (H. Sibley, undated).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The elimination and distribution of a single breath inhalation of [^{18}F]1,1,1,2-tetrafluoroethane were measured in a small group of volunteers using whole-body gamma-counting (Pike et al., 1995). Distribution was extensive, and elimination was rapid and essentially complete within 6 h (half-life $\sim 1.5\text{--}4 \text{ h}$). Elimination of radioactivity in the urine was observed in some but not all subjects, and there was no evidence of accumulation.

A group of four volunteers received 16 breath inhalations of 1,1,1,2-tetrafluoroethane (total dose 1200 mg) over a 10-min period in an investigation of its use as a propellant in medical devices (Monte et al., 1994). Urine samples were collected over a 24-h period and analysed for trifluoroacetic acid using ^{19}F nuclear magnetic resonance spectroscopy (detection limit 10 ng/ml). The amounts of trifluoroacetic acid measured in urine ranged from undetectable to 0.0004% of the administered 1,1,1,2-tetrafluoroethane. There were no other fluorinated products detected in urine using this technique.

In two inhalation studies conducted with rats, 1,1,1,2-tetrafluoroethane was poorly absorbed (Ellis et al., 1991, 1993), and elimination was rapid and achieved mainly by exhalation of unchanged 1,1,1,2-tetrafluoroethane (Finch et al., 1995). Very little metabolism occurred, with the main metabolite being carbon dioxide; trifluoroacetic acid was identified in urine. There was no significant accumulation of absorbed 1,1,1,2-tetrafluoroethane in specific tissues.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

1,1,1,2-Tetrafluoroethane has low acute toxicity. An approximate 4-h lethal concentration of 567 000 ppm (2.36×10^6 mg/m³) has been reported for rats; no effects were observed at 81 000 ppm (337 770 mg/m³) (Kennedy, 1979a, as cited in ECETOC, 1995). At concentrations in excess of 200 000 ppm (834 000 mg/m³), exposure to 1,1,1,2-tetrafluoroethane depressed the central nervous system of rats.¹ Anaesthetic effects have also been observed in other species. Cardiac sensitization (an increased sensitivity of the heart) to exogenous adrenalin has been observed in dogs exposed to 1,1,1,2-tetrafluoroethane, with a no-observed-effect level (NOEL) of 40 000 ppm (166 800 mg/m³) (Hardy et al., 1991).

8.2 Irritation and sensitization

Studies on irritation or sensitization were not available.

8.3 Short-term exposure

Information from typical short-term repeated-exposure toxicity studies was not identified.

8.4 Long-term exposure

8.4.1 Subchronic exposure

No significant exposure-related toxicological effects were observed in an inhalation study in which groups of male and female rats were exposed for 13

weeks to 1,1,1,2-tetrafluoroethane at concentrations up to 50 000 ppm (208 500 mg/m³) (Hext, 1989; Collins et al., 1995).

8.4.2 Chronic exposure and carcinogenicity

In a study conducted according to a contemporary protocol, groups of 85 male and 85 female Wistar-derived Alderley Park rats were exposed (whole-body) to 0 (air only), 2500, 10 000, or 50 000 ppm (0, 10 425, 41 700, or 208 500 mg/m³) 1,1,1,2-tetrafluoroethane, 6 h/day, 5 days/week, for 2 years (Hext & Parr-Dobrzanski, 1993; Collins et al., 1995). Mortality rates were low and similar in the control and exposed groups. No exposure-related pathological findings were recorded at interim sacrifice (52 weeks). At termination, the only exposure-related pathological findings were increased incidences of Leydig (interstitial) cell hyperplasia and benign Leydig cell adenomas in the testes. The microscopic findings in the testes occurred mainly in animals surviving to the end of the study. In the control, 2500, 10 000, and 50 000 ppm (0, 10 425, 41 700, or 208 500 mg/m³) groups, the incidence of Leydig cell hyperplasia was 27/85, 25/79, 31/85, and 40/85 (32, 32, 36, and 47%), respectively; the incidence of Leydig cell adenoma was 9/85, 7/79, 12/85, and 23/85 (11, 9, 14, and 27%), respectively. Hyperplasia was observed in most animals with such tumours. At 50 000 ppm (208 500 mg/m³) 1,1,1,2-tetrafluoroethane, the incidence of Leydig cell adenoma was significantly ($p < 0.05$) increased above the controls. The incidence of Leydig cell adenomas and hyperplasia at 10 000 ppm (41 700 mg/m³) was within the historical control levels observed at this laboratory; from 1985 to 1995, the background incidence of this tumour ranged between 4 and 19%. The no-observed-adverse-effect level (NOAEL) in this study is considered to be 10 000 ppm (41 700 mg/m³).

Other studies were less rigorously performed, but no exposure-related neoplastic or non-neoplastic effects were observed in 2-year inhalation studies (1-h daily nose-only exposure) at concentrations up to 50 000 ppm (208 500 mg/m³) in rats and up to 75 000 ppm (312 750 mg/m³) in mice (Alexander et al., 1995a) or in a similarly designed 1-year study in which dogs were exposed to 120 000 ppm (500 400 mg/m³) 1,1,1,2-tetrafluoroethane (Alexander et al., 1995b).

8.5 Genotoxicity and related end-points

The genotoxic potential of 1,1,1,2-tetrafluoroethane has been investigated in several well-conducted studies (bacterial mutagenicity [Ames] test, an *in vitro* mammalian cell cytogenetics study, an *in vivo* chromosomal aberration assay, a micronucleus study, an *in vivo* unscheduled DNA synthesis assay, and a dominant

¹ Programme for Alternative Fluorocarbon Testing, presentation at Toulouse International Toxicology Forum, September 1989; meeting notes presented as a personal communication to P. Stranding, 1993.

lethal study). 1,1,1,2-Tetrafluoroethane was not genotoxic in any of the tests (Anderson & Richardson, 1979; Hodge et al., 1979; Longstaff et al., 1984; Müller & Hofmann, 1989; Callander & Priestley, 1990; Mackay, 1990; Trueman, 1990; Collins et al., 1995).

8.6 Reproductive and developmental toxicity

No exposure-related effects were observed in a standard fertility study in which groups of rats were exposed to 0, 2500, 10 000, or 50 000 ppm (0, 10 425, 41 700, or 208 500 mg/m³) 1,1,1,2-tetrafluoroethane, 1 h/day during gametogenesis, mating, and post-mating (Alexander et al., 1996). The results from a dominant lethal study revealed no effect on fertility in male rats (Hodge et al., 1979). In a standard developmental toxicity study in rats, delayed fetal development (a statistically significant reduction in mean fetal weight, delayed ossification of digits) was observed when the dams were exposed to 50 000 ppm (208 500 mg/m³) 1,1,1,2-tetrafluoroethane; no significant exposure-related effects were observed at 10 000 ppm (41 700 mg/m³) (Hodge et al., 1980). No other exposure-related developmental effects were observed in rats at levels up to 40 000 ppm (166 800 mg/m³) 1,1,1,2-tetrafluoroethane, a concentration causing decreased maternal body weight gain in rabbits (Wickramaratne, 1989; Collins et al., 1995). In the study with rabbits, there was a 30% reduction during exposure with subsequent recovery, resulting in a net reduction in body weight of 3% compared with controls.

8.7 Immunological and neurological effects

Based upon the available evidence, specific immunological or neurological effects associated with long-term exposure to 1,1,1,2-tetrafluoroethane were not identified.

9. EFFECTS ON HUMANS

Limited data are available from an investigation into the use of 1,1,1,2-tetrafluoroethane as a propellant in a metered-dose inhaler (Donnell et al., 1995). Volunteers received up to 16 breath inhalations of 1,1,1,2-tetrafluoroethane within about 10 min. Investigations included blood pressure and heart rhythm, limited blood biochemistry, and pulmonary function tests; no abnormalities were observed, and there were no clinical signs of toxicity.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

1,1,1,2-Tetrafluoroethane has no significant effect on the growth of the bacterium *Pseudomonas putida* (6-h EC₅₀ >730 mg/litre) (Coleman & Thompson, 1990). Acute toxicity to freshwater organisms is low (*Daphnia magna*, 48-h EC₅₀ 980 mg/litre; rainbow trout *Oncorhynchus mykiss*, 96-h LC₅₀ 450 mg/litre) (Stewart & Thompson, 1990; Thompson, 1990). The high aqueous concentrations used in these studies can only be maintained artificially. In the environment, there would be rapid partitioning to the air compartment from the aqueous phase; the high concentrations used in the studies could be reached only if the atmosphere above the water were entirely 1,1,1,2-tetrafluoroethane. Additional data on toxicity of 1,1,1,2-tetrafluoroethane to aquatic or terrestrial organisms were not identified.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose-response assessment

Information on the effects of 1,1,1,2-tetrafluoroethane on humans is limited to one report; most available data on the toxicological effects of 1,1,1,2-tetrafluoroethane have been derived from studies conducted with laboratory animals. 1,1,1,2-Tetrafluoroethane exhibits relatively low toxicity. This chemical is a gas, appears to be essentially non-reactive, and is unlikely to be either an irritant or a sensitizer, although appropriate studies were not identified. A reduction in maternal body weight gain in rabbits exposed to 40 000 ppm (166 800 mg/m³) 1,1,1,2-tetrafluoroethane and signs of delayed fetal development in rats following exposure of the dams to 50 000 ppm (208 500 mg/m³) 1,1,1,2-tetrafluoroethane have been noted in developmental toxicity studies. In other toxicological investigations, adverse health effects have not been observed following exposure to concentrations up to 10 000 ppm (41 700 mg/m³) 1,1,1,2-tetrafluoroethane.

The weight of evidence for carcinogenicity of 1,1,1,2-tetrafluoroethane is limited. A statistically significant, exposure-related increase in the incidence of benign Leydig cell adenomas was observed in Wistar-derived rats exposed to a very high concentration (50 000 ppm [208 500 mg/m³]) of 1,1,1,2-tetrafluoroethane for 2 years. However, the spontaneous incidence of

these tumours is high in this and other strains of rats, and 1,1,1,2-tetrafluoroethane has not been found to be genotoxic in studies conducted to date.

11.1.2 **Criteria for setting guidance values for 1,1,1,2-tetrafluoroethane**

Based upon the available data, no adverse effects have been observed in laboratory animals exposed to 10 000 ppm (41 700 mg/m³) 1,1,1,2-tetrafluoroethane. This value can therefore serve as a basis for comparison with estimated exposure for risk characterization, either with application of appropriate uncertainty factors or directly. Examples of both approaches are presented in section 11.1.3.

11.1.3 **Sample risk characterization**

The scenario chosen as an example is the occupational environment within the United Kingdom, where, under the current conditions of use, anticipated occupational exposure (8- or 12-h time-weighted average) to 1,1,1,2-tetrafluoroethane is in the vicinity of 10 ppm (41.7 mg/m³), with occasional short-term peak exposures of up to several hundred parts per million. These concentrations are 1–3 orders of magnitude less than the NOAEL of 10 000 ppm (41 700 mg/m³) derived from toxicological studies conducted with laboratory animals. However, data on exposure in occupational circumstances within the United Kingdom are limited, and it is difficult to anticipate exposure conditions for other countries.

A health-based occupational exposure limit for 1,1,1,2-tetrafluoroethane of 1000 ppm (4170 mg/m³) (8-h time-weighted average) has been established within the United Kingdom. This equates to division of the NOAEL of 10 000 ppm (41 700 mg/m³) by an uncertainty factor of 10.

11.2 **Evaluation of environmental effects**

The low toxicity of 1,1,1,2-tetrafluoroethane to the few aquatic organisms tested as well as its high volatility indicate negligible risk to aquatic organisms.

Atmospheric effects have been assessed by modelling. Recent observations have shown a rapid increase in atmospheric concentrations of 1,1,1,2-tetrafluoroethane, mainly as a result of emissions over the past decade. Modelling indicates insignificant ozone depletion potential, a significant global warming potential, and negligible acidification potential.

12. **PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES**

Previous evaluations of 1,1,1,2-tetrafluoroethane by international bodies were not identified. Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

13. **HUMAN HEALTH PROTECTION AND EMERGENCY ACTION**

Human health hazards, together with preventative and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 1281) reproduced in this document.

13.1 **Human health hazards**

1,1,1,2-Tetrafluoroethane is essentially non-toxic and flammable. There is a possibility of frostbite if the liquefied gas is released rapidly.

13.2 **Advice to physicians**

Symptomatic treatment and supportive therapy should be provided as indicated. Adrenaline and similar sympathomimetic drugs should be avoided following exposure, as cardiac arrhythmia may result, with possible subsequent cardiac arrest.

13.3 **Spillage**

In the event of spillage of 1,1,1,2-tetrafluoroethane, emergency crews should wear proper personal protection, including respiratory protection. Because the vapour is heavier than air, it may accumulate in lower spaces, causing a deficiency of oxygen. The oxygen content of the air should always be checked before the affected area is entered.

14. **CURRENT REGULATIONS, GUIDELINES, AND STANDARDS**

Information on national regulations, guidelines, and standards can be found in the International Register of Potentially Toxic Chemicals (IRPTC), available from UNEP Chemicals (IRPTC), Geneva.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

1,1,1,2-TETRAFLUOROETHANE

1281

March 1998

CAS No: 811-97-2
RTECS No: KI8842500
UN No: 3159

HFC 134a
 $C_2H_2F_4$
Molecular mass: 102.03

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames. NO contact with hot surfaces.	In case of fire in the surroundings: all extinguishing agents allowed.
EXPLOSION			In case of fire: keep cylinder cool by spraying with water.

EXPOSURE			
Inhalation	Dizziness. Drowsiness. Dullness.	Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	ON CONTACT WITH LIQUID: FROSTBITE.	Cold-insulating gloves.	ON FROSTBITE: rinse with plenty of water, do NOT remove clothes.
Eyes		Safety goggles.	
Ingestion			

SPILLAGE DISPOSAL	PACKAGING & LABELLING
NEVER direct water jet on liquid. Do NOT let this chemical enter the environment. Chemical protection suit including self-contained breathing apparatus.	UN Hazard Class: 2.2

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-20G39	Fireproof. Keep in a well-ventilated room.

IMPORTANT DATA

Physical State; Appearance

COMPRESSED LIQUEFIED GAS, WITH CHARACTERISTIC ODOUR.

Chemical dangers

On contact with hot surfaces or flames this substance decomposes forming toxic and corrosive fumes.

Occupational exposure limits

TLV not established. MAK not established.

Routes of exposure

The substance can be absorbed into the body by inhalation.

Inhalation risk

A harmful concentration of this gas in the air will be reached very quickly on loss of containment.

Effects of short-term exposure

Rapid evaporation of the liquid may cause frostbite. The substance may cause effects on the central nervous system and cardiovascular system, resulting in cardiac disorders.

PHYSICAL PROPERTIES

Boiling point: -26°C
Melting point: -101°C
Solubility in water: none

Vapour pressure, kPa at 25°C: 630
Relative vapour density (air = 1): 3.5
Octanol/water partition coefficient as log Pow: 1.06

ENVIRONMENTAL DATA

Avoid release to the environment in circumstances different to normal use.

NOTES

Do NOT use in the vicinity of a fire or a hot surface, or during welding. Turn leaking cylinder with the leak up to prevent escape of gas in liquid state.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

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APPENDIX 1 — SOURCE DOCUMENT

Standing et al. (1995)

The draft report entitled *1,1,1,2-Tetrafluoroethane; Criteria document for an occupational exposure limit* (prepared by P. Standing, S. Maidment, A. Ogunbiyi, J. Groves, and J. Cocker) was initially reviewed internally by a group of approximately 10 Health and Safety Executive experts (mainly toxicologists, but also experts in other relevant disciplines, such as epidemiology and occupational hygiene). The toxicology section of the amended draft was then reviewed by toxicologists from the United Kingdom Department of Health. Subsequently, the entire criteria document was reviewed by a tripartite advisory committee to the United Kingdom Health and Safety Commission, the Working Group for the Assessment of Toxic Chemicals (WATCH). This committee is composed of experts in toxicology and occupational health and hygiene from industry, trade unions, and academia.

Members of the WATCH committee at the time of the peer review were Mr S. Bailey, Independent Consultant; Professor J. Bridges, University of Surrey; Dr I. Guest, Chemical Industries Association; Dr A. Hay, Trade Unions Congress; Dr L. Levy, Institute of Occupational Hygiene, Birmingham; Dr M. Molyneux, Chemical Industries Association; Mr A. Moses, Chemical Industries Association; Dr R. Owen, Trade Unions Congress; and Mr J. Sanderson, Independent Consultant.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 1,1,1,2-tetrafluoroethane was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

Department of Health, London, United Kingdom

Department of Public Health, Albert Szent-Gyorgyi University Medical School, Szeged, Hungary

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium

Health Canada, Ottawa, Canada

International Agency for Research on Cancer, Lyon, France

Ministry of Health and Welfare, International Affairs Division, Government of Japan, Tokyo, Japan

National Institute for Working Life, Solna, Sweden

National Institute of Occupational Health, Budapest, Hungary

United States Department of Health and Human Services (National Institute of Environmental Health Sciences)

United States Environmental Protection Agency (Office of Pollution Prevention and Toxics; National Center for Environmental Assessment, Office of Research and Development; Office of Drinking Water)

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Berlin, Germany, 26–28 November 1997

Members

Dr H. Ahlers, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Mr R. Cary, Health Directorate, Health and Safety Executive, Bootle, United Kingdom

Dr S. Dobson, Institute of Terrestrial Ecology, Huntingdon, United Kingdom

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany (*Chairperson*)

Mr J.R. Hickman, Health Protection Branch, Health Canada, Ottawa, Ontario, Canada

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Mr D. Renshaw, Department of Health, London, United Kingdom

Dr J. Sekizawa, Division of Chemo-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Prof. S. Soliman, Department of Pesticide Chemistry, Alexandria University, Alexandria, Egypt (*Vice-Chairperson*)

Dr M. Wallen, National Chemicals Inspectorate (KEMI), Solna, Sweden

Ms D. Willcocks, Chemical Assessment Division, Worksafe Australia, Camperdown, Australia

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Observers

Mrs B. Dinham,¹ The Pesticide Trust, London, United Kingdom

Dr R. Ebert, KSU Ps-Toxicology, Huels AG, Marl, Germany (representing ECETOC, the European Centre for Ecotoxicology and Toxicology of Chemicals)

Mr R. Green,¹ International Federation of Chemical, Energy, Mine and General Workers' Unions, Brussels, Belgium

Dr B. Hansen,¹ European Chemicals Bureau, European Commission, Ispra, Italy

Dr J. Heuer, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Mr T. Jacob,¹ DuPont, Washington, DC, USA

Ms L. Onyon, Environment Directorate, Organisation for Economic Co-operation and Development, Paris, France

Dr H.J. Weideli, Ciba Speciality Chemicals Inc., Basel, Switzerland (representing CEFIC, the European Chemical Industry Council)

Secretariat

Dr M. Baril, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr R.G. Liteplo, Health Canada, Ottawa, Ontario, Canada

Ms L. Regis, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr A. Strawson, Health and Safety Executive, London, United Kingdom

Dr P. Toft, Associate Director, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

¹ Invited but unable to attend.

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au 1,1,1,2-tétrafluoréthane est fondé sur une étude des problèmes de santé (notamment dans le domaine de l'hygiène du travail) réalisée par le Health and Safety Executive du Royaume-Uni en 1995 (Strandring et al., 1995). Des informations complémentaires concernant les effets de cette substance sur la santé humaine et l'environnement ont été identifiées dans l'étude ECETOC (1995). Ces deux études prennent en compte les données antérieures à décembre 1994. Les données postérieures à leur publication ont été incorporées dans le présent document. Les informations relatives à l'examen du document initial par les pairs et à sa disponibilité figurent à l'appendice 1. Les renseignements concernant l'examen du CICAD par les pairs font l'objet de l'appendice 2. Ce CICAD a été approuvé tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Berlin (Allemagne) du 26 au 28 novembre 1997. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information sur la sécurité chimique du 1,1,1,2-tétrafluoréthane (ICSC 1281), établie par le Programme international sur la Sécurité chimique (IPCS, 1998), est également reproduite dans le présent document.

Le 1,1,1,2-tétrafluoréthane (CAS N° 811-97-2) est un fluorocarbure gazeux obtenu par réaction du fluorure d'hydrogène sur le trichloréthylène en vase clos. Il est utilisé principalement comme réfrigérant dans des appareils fonctionnant à température relativement élevée, comme les réfrigérateurs domestiques et les climatiseurs d'automobiles. Il peut également être employé dans la fabrication de mousses plastiques, comme solvant pour certaines opérations de nettoyage, comme propulseur d'aérosols pour inhalateurs médicaux, et comme produit extincteur à la place des halons.

On dispose de peu d'informations sur l'exposition du grand public ou des travailleurs au 1,1,1,2-tétrafluoréthane. Le personnel employé à sa fabrication au Royaume-Uni a été soumis à une très faible exposition, les concentrations ne dépassant jamais 7 ppm (29,2 mg/m³). L'exposition résultant de son utilisation dans l'industrie manufacturière n'a pas été mesurée et l'on ne dispose pas de données concernant l'exposition des personnels appelés à l'utiliser sur le terrain. Compte tenu de la situation sur les lieux de travail au Royaume-Uni, et par analogie avec les données obtenues lors d'une étude de l'exposition au dichlorotrifluoréthane (HCFC 123), il semble que la concentration de 1,1,1,2-tétrafluoréthane sur les lieux de travail soit normalement faible (inférieure à 10 ppm, soit 41,7 mg/m³), avec parfois des pics d'exposition de courte durée atteignant quelques centaines de parties par million.

Les renseignements concernant les effets du 1,1,1,2-tétrafluoréthane sur l'homme se limitent à une étude; la plupart des données disponibles sur les effets toxicologiques de cette substance ont été obtenues à partir d'expériences chez l'animal. Le 1,1,1,2-tétrafluoréthane a une toxicité relativement faible. Des études visant à évaluer sa toxicité pour le développement font état d'un ralentissement du gain pondéral chez des lapines exposées à 40 000 ppm (166 800 mg/m³) et d'un retard de développement des fœtus chez des rates exposées à 50 000 ppm (208 500 mg/m³). D'autres études toxicologiques ne signalent aucun effet défavorable chez des animaux exposés à des concentrations allant jusqu'à 10 000 ppm (41 700 mg/m³). Les indices de cancérogénicité se limitent à une incidence accrue des adénomes des cellules de Leydig après exposition à 50 000 ppm (208 500 mg/m³); d'autre part, les études menées jusqu'à présent ne révèlent aucun signe de génotoxicité.

La faible toxicité du 1,1,1,2-tétrafluoréthane pour les quelques organismes aquatiques sur lesquels il a été testé et sa grande volatilité donnent à penser qu'il constitue un risque négligeable pour ces organismes.

Les effets du 1,1,1,2-tétrafluoréthane sur l'atmosphère ont été évalués à l'aide de modèles. Des observations récentes ont révélé une augmentation rapide de sa concentration atmosphérique, résultant principalement des émissions qui ont eu lieu au cours de la dernière décennie. Les résultats de la modélisation montrent que le 1,1,1,2-tétrafluoréthane présente un risque insignifiant en ce qui concerne la destruction de l'ozone, un risque significatif pour ce qui est du réchauffement mondial et un risque négligeable d'acidification.

RESUMEN DE ORIENTACIÓN

Este CICAD (resumen de evaluación internacional de sustancias químicas) sobre el 1,1,1,2-tetrafluoroetano está basado en un estudio sobre su posible incidencia (fundamentalmente ocupacional) en la salud humana preparado por la Dirección de Salud y Seguridad del Reino Unido en 1995 (Standring et al., 1995). En el ECETOC (1995) se halló más información sobre los efectos en la salud humana y en el medio. Los datos manejados en esos dos estudios abarcan hasta diciembre de 1994. También se ha incluido cuando procedía información adicional hallada tras la publicación de esos estudios. En el apéndice 1 se informa sobre la naturaleza del examen colegiado y la disponibilidad del documento de base, y en el apéndice 2 se facilita información sobre el examen colegiado del presente resumen. Este CICAD fue aprobado como resumen de evaluación internacional en una reunión de la Junta de Revisión Final celebrada en Berlín (Alemania) los días 26 a 28 de noviembre de 1997. La lista de los participantes en la reunión de la Junta de Revisión Final figura en el apéndice 3. En este documento se reproduce también la ficha internacional de seguridad química (ICSC 1281) para el 1,1,1,2-tetrafluoroetano, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1998).

El 1,1,1,2-tetrafluoroetano (CAS nº 811-97-2) es un fluorocarburo gaseoso que se fabrica haciendo reaccionar el ácido fluorhídrico y el tricloroetileno en un sistema cerrado. Se usa fundamentalmente como refrigerante para el enfriamiento de “alta temperatura,” por ejemplo en los frigoríficos domésticos y en los sistemas de aire acondicionado de los automóviles. Otros usos posibles son su empleo en espumación, como disolvente en aplicaciones de limpieza especiales, como propulsor de aerosoles para inhaladores médicos y como extintor de incendios en lugar de los halones.

La información hallada sobre la exposición del público general o los trabajadores al 1,1,1,2-tetrafluoroetano es escasa. Durante su fabricación en el Reino Unido, la exposición de los empleados a ese producto fue muy baja, y las concentraciones medidas no superaron en ningún caso las 7 ppm (29,2 mg/m³). No se dispone de datos sobre la exposición asociada a su uso en la industria fabril, ni sobre la exposición del personal de servicios sobre el terreno. La situación en los lugares de trabajo en el Reino Unido y otros datos análogos de un solo estudio de exposición al diclorotrifluoroetano (HCFC 123) parecen indicar que la exposición al 1,1,1,2-tetrafluoroetano en el lugar de trabajo es normalmente baja (es decir, inferior a 10 ppm [41,7 mg/m³]),

registrándose ocasionalmente exposiciones máximas breves de hasta varios cientos de partes por millón.

Sólo hay un informe que trate de los efectos del 1,1,1,2-tetrafluoroetano en el ser humano; la mayor parte de los datos disponibles sobre sus efectos toxicológicos proceden de estudios realizados en animales de laboratorio. El 1,1,1,2-tetrafluoroetano tiene una toxicidad relativamente baja. Los estudios sobre su toxicidad en el desarrollo han mostrado una reducción del aumento del peso corporal materno en conejos expuestos a 40 000 ppm (166 800 mg/m³) de 1,1,1,2-tetrafluoroetano, así como signos de retraso del desarrollo fetal en ratas tras la exposición de las madres a concentraciones de 50 000 ppm (208 500 mg/m³). En otras investigaciones toxicológicas no se han observado efectos adversos para la salud tras la exposición a concentraciones de hasta 10 000 ppm (41 700 mg/m³). Los indicios de carcinogenicidad se limitan a un aumento de la incidencia de adenomas de las células de Leydig tras la exposición a 50 000 ppm (208 500 mg/m³), y no se han detectado efectos genotóxicos en los estudios realizados hasta la fecha.

La baja toxicidad del 1,1,1,2-tetrafluoroetano para los escasos organismos acuáticos analizados, así como su elevada volatilidad, indican que el riesgo es insignificante para los organismos acuáticos.

Se han elaborado modelos para evaluar los efectos atmosféricos. Observaciones recientes han puesto de manifiesto un rápido incremento de las concentraciones atmosféricas de 1,1,1,2-tetrafluoroetano, principalmente como resultado de las emisiones realizadas a lo largo del último decenio. La modelización ha revelado una desdeniable contribución potencial al agotamiento del ozono, una considerable capacidad de contribución al calentamiento mundial y un potencial de acidificación despreciable.