

ANNEX 6

ANNOTATED EXAMPLE CICAD

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

**CONCISE INTERNATIONAL CHEMICAL ASSESSMENT
DOCUMENT**

The title page should indicate the programme, name of the chemical, the stage of preparation of the draft CICAD (e.g., in this case post-peer review) as well as the date of the draft document.

1,1,2,2-TETRACHLOROETHANE

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Post-Peer Review Draft

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CONTENTS

FOREWORD.....
1. EXECUTIVE SUMMARY
2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES
3. ANALYTICAL METHODS.....
4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE.....
5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION
6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE.....
6.1 Environmental levels
6.2 Human exposure
7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS.....
8. EFFECTS ON LABORATORY MAMMALS AND <i>IN VITRO</i> TEST SYSTEMS.....
8.1 Single exposure.....
8.2 Short-term exposure
8.3 Medium-term exposure.....
8.4 Long-term exposure and carcinogenicity.....
8.5 Genotoxicity and related end-points.....
8.6 Reproductive toxicity
8.6.1 Effects on fertility.....
8.6.2 Developmental toxicity
8.7 Other toxicity.....
8.8 Mode of action.....
9. EFFECTS ON HUMANS.....
10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD.....
10.1 Aquatic environment
10.2 Terrestrial environment.....
11. EFFECTS EVALUATION
11.1 Evaluation of health effects
11.1.1 Hazard identification and dose–response assessment.....
11.1.2 Criteria for setting tolerable intakes and guidance values
11.1.3 Sample risk characterization
11.1.3.1 Exposure of the sample population.....
11.1.3.2 Health risks in the sample population.....
11.1.4 Uncertainties in the evaluation of health risks
11.2 Evaluation of environmental effects
12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES
REFERENCES
APPENDIX 1 — SOURCE DOCUMENTS.....
APPENDIX 2 — CICAD PEER REVIEW
APPENDIX 3 - CICAD FINAL REVIEW BOARD.....
INTERNATIONAL CHEMICAL SAFETY CARD
TABLES

This is the standard format for all CICADs.

Authors should adhere to the standard format to the extent possible, using the designated heading and subheadings in preparation of the draft CICAD.

Alterations to the standard format may be undertaken only when warranted (for example, where there might be no data on environmental effects, the subsections 10.1, 10.2 and 11.2 need not be included. Tables (numbered sequentially) should be grouped together at the end of the draft document and not presented within the body of the text.

Appendix 1 should be included by authors in draft CICADs submitted for primary review by IPCS and international peer review.

Appendix 2 will be included by the Secretariat in subsequent drafts submitted for Final Review Board review and approval, and publication.

Appendix 3 lists members of the Final Review Board, it is prepared by the Secretariat and inserted into the finalized CICAD prior to publication.

The relevant international Chemical Safety Card/s will be inserted at the end of the document by the Secretariat.

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 Organization (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.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. 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

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.

The FOREWORD outlines the function of CICADs and the process by which they are prepared and reviewed.

The FOREWORD is inserted in the CICAD template provided by the Secretariat

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) (also available at <http://www.who.int/pcs/>).

Procedures

The flow chart [Annex 5] 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 IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure, and/or
- significant toxicity/ecotoxicity

Thus a priority chemical typically

- is of transboundary concern
- is of concern to a range of countries for possible risk management: developed, developing and those with economies in transition
- is significantly traded internationally
- has high production volume
- has dispersive use

The Steering group will also advise IPCS on the appropriate form of the document (*i.e.*, EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

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, as necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science.

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 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

1. This CICAD on 1,1,2,2-tetrachloroethane was prepared by the Environmental Health Directorate of Health Canada and was based principally on a review prepared by the Government of Canada (1993) to assess the potential effects on human health of indirect exposure to 1,1,2,2-tetrachloroethane in the general environment and the chemical's environmental effects, as well as a review prepared by the Agency for Toxic Substances and Disease Registry (ATSDR, 1994) intended to characterize information on adverse health effects and public exposure. Data identified as of September 1992 were considered in the Government of Canada (1993) review. A comprehensive literature search of several on-line databases was conducted in August 1995 to identify any references published subsequent to those incorporated in this review. Information on the nature of the peer review and the availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. The International Chemical Safety Card (ICSC 0332) for 1,1,2,2-tetrachloroethane, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

2. 1,1,2,2-Tetrachloroethane (CAS no. 79-34-5) is a volatile synthetic chemical that is used principally as an intermediate in the synthesis of other chlorinated hydrocarbons, although use of this substance has declined significantly. Releases to the environment are primarily in emissions to ambient air, where the chemical is likely to remain for several weeks. 1,1,2,2-Tetrachloroethane is not expected to contribute to the depletion of stratospheric ozone or to global warming. It is rapidly removed from aquatic systems and is unlikely to bioaccumulate. Human exposure to 1,1,2,2-tetrachloroethane is principally via inhalation.

3. Very few data are available on the effects of exposure to 1,1,2,2-tetrachloroethane in humans. The toxicological profile of 1,1,2,2-tetrachloroethane has also not been well characterized; because of the chemical's declining use, available data are confined primarily to early limited studies. The acute toxicity of 1,1,2,2-tetrachloroethane in experimental animals is slight to moderate. Based on the results of principally limited short-term and subchronic studies, the liver appears to be the most sensitive target organ. Although most of the available studies are inadequate to allow a no- or lowest-observed-(adverse)-effect level

The Executive Summary provides a brief overview of the preparation of the CICAD, as well as the critical data and conclusions.

Information presented in the first paragraph of this section should include:

- identification of the background source document(s) upon which the CICAD is based and the cut-off date of literature review for the source document and for any additional subsequent literature review conducted in preparing the CICAD

- reference to the nature of the peer review and availability of the source document(s), [outlined in Appendix 1 of the CICAD]

- reference to the list of individuals and institutions from which peer review comments were received [outlined in Appendix 2 of the CICAD]

- reference to the accompanying International Chemical

[NO(A)EL or LO(A)EL] for hepatotoxicity to be determined with confidence, minimal effects on the liver (reversible increase in lipid content) and other end-points (an increase in levels of adrenocorticotrophic hormone and reversible alterations in haematological parameters) have been observed in rats exposed to 13.3 mg/m³ for up to 9 months. Based on limited, primarily range-finding studies and early investigations, reproductive and developmental effects have been observed in experimental animals only at doses that caused reductions in body weight.

4. Long-term ingestion of 1,1,2,2-tetrachloroethane resulted in an increased incidence of liver tumours in both male and female B6C3F₁ mice. However, similar exposure was not associated with a significant increase in tumours at any site in Osborne-Mendel rats, although both species were exposed only for up to 78 weeks. Based on the results of available *in vivo* and *in vitro* assays, 1,1,2,2-tetrachloroethane has, at most, weak genotoxic potential. 1,1,2,2-Tetrachloroethane was a potent promoter, but not an initiator, of -glutamyltranspeptidase-positive foci in the liver of rats. The profile for tumour induction by 1,1,2,2-tetrachloroethane is similar to that of dichloroacetic acid, its primary metabolite. Information on the mechanism of tumour induction by 1,1,2,2-tetrachloroethane is incomplete; for several of its metabolites, it has been suggested that tumours are likely induced by mechanisms for which there is a threshold.

5. Exposure to 1,1,2,2-tetrachloroethane has been demonstrated to inhibit the activities of environmental bacteria (the lowest reported IC₅₀ was 1.4 mg/litre) and cause immobilization in *Daphnia magna* (48-hour EC₅₀ values of 23 mg/litre and above). In freshwater fish species, the lowest reported LC₅₀ (96 hours) was 18.5 mg/litre in flagfish (*Jordanella floridae*), whereas the lowest-observed-effect concentration (LOEC) for longer-term exposure was 7.2 mg/litre, which resulted in reduced larval survival in the same species. No data were identified on the effects of this substance on terrestrial organisms.

6. In order to provide guidance to relevant authorities, sample guidance values have been determined on the basis of the potency of 1,1,2,2-tetrachloroethane to induce liver tumours in mice, as this is the toxicological end-point for which the dose-response relationship is best characterized. It is noted, however, that observed increases in tumour incidence are currently restricted to one species and that there are suggestive but incomplete data indicating that tumours may be induced by a non-genotoxic mechanism. The potency, expressed as the dose associated with a 5% increase in tumours, ranged from 5.8 to 28 mg/kg body weight per day. Sample guidance values for air (the principal source of human exposure), calculated on the basis of division of this potency range by 5000 or 50 000, are 3.4–16 µg/m³ and 0.34–1.6 µg/m³. These values correspond to those considered by some agencies to represent “essentially negligible” risk (i.e. 10⁻⁵ to 10⁻⁶) for a genotoxic carcinogen; it should be noted, however, that a smaller margin may also be appropriate in view of the suggestive but incomplete evidence for an epigenetic mechanism of tumour induction. Corresponding values for ingestion are 1.2–5.6 µg/kg body weight per day and 0.12–0.56 µg/kg body weight per day. Based on a sample estimate of exposure, indirect exposure in the general environment is less than these values, which are considered to be conservative in view of the suggestive but incomplete evidence that 1,1,2,2-tetrachloroethane may induce tumours through a threshold mechanism.

Safety Card(s) reproduced in the CICAD

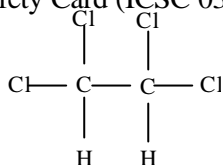
As appropriate, the use of standard text (as shown) when referring in the Executive Summary, to Appendices 1 & 2 and the International Chemical Safety Card reproduced therein, is encouraged.

Système International d'Unités (SI units) should be used throughout the CICAD. Where units of measurement are presented as ppm, ppb, etc, in the original citation, the appropriate conversion to SI units (in parenthesis) should also be provided.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

1,1,2,2-Tetrachloroethane (CAS no. 79-34-5; $C_2H_2Cl_4$; acetylene tetrachloride, *sym*-tetrachlorethane; see structural diagram below) is a synthetic chemical that is a colourless, non-flammable liquid at room temperature. It is highly volatile, with a vapour pressure of 0.65 kPa at 20 C and water solubility of 2900 mg/litre at 20 C. The log octanol/water partition coefficient for 1,1,2,2-tetrachloroethane is about 2.5, whereas its Henry's law constant was determined to range from 0.0003 to 0.0009 $m^3 \cdot atm/mol$ (Tse et al., 1992; Government of Canada, 1993; Nichols et al., 1993). Additional physical/chemical properties are presented in the International Chemical Safety Card (ICSC 0332) reproduced in this document.

Structural formula:



Section 2 provides a brief overview of the more relevant physical and chemical properties related to assessing the hazards and risks of the chemical to humans and environmental organisms.

Information presented in this section should include: chemical name; CAS number; chemical formula; molecular mass; two to three common synonyms; information on properties relevant to prediction of fate in the environment (i.e., as applicable, volatility, aqueous solubility, Henry's law constant [dimensionless & with dimensions], octanol-water partition coefficient)
- conversion factor [cm^3/m^3 (ppm) to mg/m^3] at 20°C and 101 kPa
- structural formula.

Additional relevant information such as data on the purity or chemical form (e.g., hydrochloride salt) of the chemical commonly examined in toxicological studies may also be mentioned here.

Additional physical/chemical properties are outlined in the International Chemical Safety Card. The use of the standard text (as shown) when referring to the International Chemical Safety Card in this section is encouraged

3. ANALYTICAL METHODS

1. Analysis of 1,1,2,2-tetrachloroethane in air usually involves preconcentration on a sorbent tube followed by thermal or solvent desorption or collection in a cryogenically cooled trap followed by gas chromatography (flame ionization or electron capture detection). Detection limits range from 0.7 ng/m³ to 0.3 mg/m³ (ATSDR, 1994). Purge and trap methods followed by gas chromatography (flame ionization, electron capture electrolytic conductivity, or microcoulometric detection) are generally used for water as well as sediment, soil, or other solid samples. Reported detection limits range from 0.001 to 5 µg/litre for water and from 1 to 5 µg/kg for soil and sediment samples (ATSDR, 1994). Detection limits of 0.01 µg/litre and 0.06 ppbv (0.4 µg/m³) have been reported for solid-phase microextraction coupled with gas chromatography/ion trap mass spectrometry analysis for water and air samples, respectively (Arthur et al., 1992; Chai & Pawliszyn, 1995). Gas chromatography, often in combination with mass spectrometry, is commonly used for quantifying 1,1,2,2-tetrachloroethane in biological samples, with detection limits of 400 µg/kg in tissues and 5–500 ng/litre in blood (ATSDR, 1994).

Section 3 provides a summary of the most commonly used methods to quantify the chemical in environmental and biological samples.

The inclusion of detection limits is a key feature of the information provided in this section and an indication of the accuracy (trueness, precision, recovery) is useful.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

1. There are no known natural sources of 1,1,2,2-tetrachloroethane. The principal use of 1,1,2,2-tetrachloroethane is as an intermediate in the manufacture of other chlorinated hydrocarbons, such as vinyl chloride, 1,2-dichloroethane, trichloroethylene, and tetrachloroethylene; in the past, it was also used as an industrial solvent and as a pesticide. Use, and hence production, of 1,1,2,2-tetrachloroethane has declined significantly; no recent data on production were identified. Releases to the atmosphere through its use as a chemical intermediate in Canada in 1990 were estimated to be approximately 246 kg (Government of Canada, 1993), whereas 64 251 pounds (29 144 kg) were estimated to be emitted to air from reporting industries in the USA in 1991 (ATSDR, 1994). In 1991, 953 kg of 1,1,2,2-tetrachloroethane were discharged to water from reporting facilities in the USA (ATSDR, 1994).

Section 4 provides an overview on the occurrence (i.e., natural and anthropogenic), use patterns, production (including data on trends) and emissions of the chemical into the environment, quantified where feasible.

ADDITIONAL EXAMPLE

2 Global production of methyl methacrylate was estimated to be 1.4 million tonnes in 1988 (IARC, 1994). In the USA and Japan, production of methyl methacrylate ranged from 380 000 to 536 000 t and from 384 000 to 403 000 t, respectively, between 1990 and 1992 (IARC, 1994). Total production volume within the European Union was 447 000 t in 1993 (CEFIC, 1994).

Data on production of the chemical should be summarized within the text in the following order; world-wide, region-wide or within specific countries. Data on releases into specific media that serve as sources of human and environmental exposure should similarly be summarised world-wide, region-wide or within specific countries. Data should be expressed in kilograms (kg) or metric tonnes

3. Methyl methacrylate can enter the environment during its transport, bulk storage, and use. Based on data from the US Toxic Chemical Release Inventory, emissions to air, water, and soil from industries in the USA are estimated to be about 0.46% of production. Most of the released methyl methacrylate (i.e. 98%) is estimated to be emitted to air, with very small amounts being released into water and soil. Data on emissions of methyl methacrylate in other countries have not been identified. Assuming a production in the USA in 1992 of approximately 500 000 t (IARC, 1994), approximately 2300 t are estimated to have been released to the environment.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

1. 1,1,2,2-Tetrachloroethane is released to the environment primarily in emissions to ambient air. Based on its vapour pressure, it is not likely to be transferred to other compartments. The atmospheric lifetime for 1,1,2,2-tetrachloroethane reacting with hydroxyl radicals from moderately polluted areas is estimated to be between 43 and 100 days, based on estimated and measured reaction rates, respectively (Government of Canada, 1993). The half-life in the troposphere is estimated to be in excess of 800 days, and diffusion into the stratosphere is expected to be slow. Based on these estimates, there is significant potential for long-range transport of 1,1,2,2-tetrachloroethane. In the stratosphere, 1,1,2,2-tetrachloroethane undergoes photolysis to produce chlorine radicals, which may subsequently react with ozone; however, the ozone depletion potential for 1,1,2,2-tetrachloroethane is very much less than 0.001 relative to the standard CFC-11 (trichlorofluoromethane), based on the method developed by Nimitz & Skaggs (1992).

2. 1,1,2,2-Tetrachloroethane released to the aquatic environment is rapidly removed via volatilization, with an estimated half-life of 6.2 hours from running water and 3.5 days from still water. Hydrolysis and biodegradation are the principal routes of removal from ground water. The hydrolysis half-life in subsurface sediment at 25 C was determined to be 29 days (Haag & Mill, 1988). Neutral and base-catalysed hydrolyses of 1,1,2,2-tetrachloroethane in pure water yielded trichloroethylene as essentially the sole degradation product (Haag & Mill, 1988). The products of anaerobic biodegradation of 1,1,2,2-tetrachloroethane were determined in a 6-week study to be (in decreasing order) *cis*-1,2-dichloroethylene, *trans*-1,2-dichloroethylene, trichloroethylene, 1,1,2-trichloroethane, 1,1-dichloroethylene, and vinyl chloride (Hallen et al., 1986).

3. 1,1,2,2-Tetrachloroethane is not expected to bioaccumulate in aquatic species, based on low measured and calculated bioconcentration factors

ADDITIONAL EXAMPLE

4. A Level I fugacity model in an evaluative environment predicts the following equilibrium partitioning of methyl methacrylate: air, 86.6%; water, 13.1%; and soil/sediment, <0.4% (Mackay et al., 1995). in fish (Government of Canada, 1993).

ADDITIONAL EXAMPLE

5. 3,3'-Dichlorobenzidine can accumulate in aquatic biota. A bioconcentration factor of approximately 500 has been reported for bluegill sunfish (*Lepomis macrochirus*), based on a study in which the fish were exposed to 5 or 100 µg [¹⁴C]3,3'-dichlorobenzidine per litre; equilibria were achieved within 96–168 hours (Appleton & Sikka, 1980). In other studies, a 3-day bioaccumulation factor of 610 in fish (golden orfe, *Leuciscus idus melanotus*), a 5-day bioaccumulation factor of 3100 in activated sludge, and a 1-day bioaccumulation factor of 940 in algae (*Chlorella fusca*) have been reported (Freitag et al., 1985).

Section 5 provides an overview of the fate of the chemical in the environment including sinks, persistence and potential for bioaccumulation.

In cases where data on the distribution of the chemical are not available, the inclusion of predicted distributions derived from models cited in the published literature is encouraged

Where this is done, its limitations, as well as the assumptions and input data used in deriving the parameters reported, must be clearly outlined within the text. (See also the use of modelling to predict environmental concentrations in section 6.1)

In cases where the chemical is likely to accumulate, relevant data on bioconcentration factors (BCFs) should be summarized briefly. If no BCFs are available, an indication of accumulation tendency should be given, based on the log P_{ow} .

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

1. Data considered to be most representative of current levels of 1,1,2,2-tetrachloroethane in environmental media are presented in Table 1. Mean concentrations of 1,1,2,2-tetrachloroethane in recent surveys of ambient air in cities in Canada ranged from <0.1 to 0.25 µg/m³. Maximum concentrations of up to 79 µg/m³ have been detected in the vicinity of waste sites in the USA (ATSDR, 1994).
2. Although data are limited, levels of 1,1,2,2-tetrachloroethane in surface waters in Canada, the USA, and Germany generally range from <0.005 to 4 µg/litre, from <10 µg/litre to a maximum reported value of 180 µg/litre, and from <0.03 to 10 µg/litre, respectively; the chemical was not detected (detection limits 0.001–0.05 µg/litre) in surface waters in Japan.
3. 1,1,2,2-Tetrachloroethane was not detected in sediment in Japan in 1976 (detection limits ranged from 0.05 to 1 µg/g dry weight).

Section 6.1 provides an overview of the concentrations of the chemical that might be found in environmental media, and media through which humans may be exposed: ambient air (rural & urban), indoor air including occupational exposure, surface and ground water, soils, sediments, and biota, drinking water.

When important in judging the concentrations reported, the methods should be indicated. For non-detectable concentrations, the detection limits should be specified.

ADDITIONAL EXAMPLE

4. Data on environmental levels of limonene are presented in Table 2. The concentrations of limonene and other monoterpenes in air vary considerably. Recorded concentrations in rural areas depend on many factors, such as the type of vegetation, temperature, time of the day, and time of the year (Strömvall, 1992). Biogenic monoterpene emissions are assumed to be very low in the late autumn and winter months compared with summer (Altshuller, 1983). Measured concentrations (between 1979 and 1992) of limonene in the air of rural forest areas in Europe, Canada, the USA, Nepal, the Republic of Georgia, and Japan ranged from 1.6×10^{-4} to 2.2 ppb (0.9 ng/m³ to 12.2 µg/m³) (Shaw et al., 1983; Hutte et al., 1984; Roberts et al., 1985; Jüttner, 1986, 1988; Petersson, 1988; Helmig et al., 1989; Clement et al., 1990; Janson & Kristensson, 1991; Ciccoioli et al., 1992, 1993; Helmig & Arey, 1992; Peters et al., 1994). Based upon these data, typical concentrations of limonene in air from rural areas range from 0.1 to 0.2 ppb (0.6–1.1 µg/m³).
5. On the basis of measured concentrations (between 1973 and 1990) of limonene in the air from urban or suburban areas in Europe, the USA, and Russia that ranged from not detectable to 5.7 ppb (31.7 µg/m³) (Bertsch et al., 1974; Ioffe et al., 1977, 1979; Hutte et al., 1984; De Bortoli et al., 1986; Jüttner, 1988; Ciccoioli et al., 1992; Helmig & Arey, 1992), typical concentrations of limonene in urban/suburban air are likely to range from 0.1 to 2 ppb (0.6–11.1 µg/m³). Concentrations of limonene in air emissions from kraft pulp industries, stone groundwood production, and various waste and landfill sites have ranged from approximately 0.3 to 41 000 ppb (1.7 µg/m³ to 240 mg/m³) (Young & Parker, 1983, 1984; Koe & Ng, 1987; Strömvall, 1992; Eitzer, 1995).

Where available data are extensive, information from national surveys may be summarized in tabular format (see Tables 1 & 2 at the end of this annex for examples), with the general range of observed concentrations in air, water (etc), presented within the text (see example of limonene).

6. Limonene has been detected in ground water and surface waters, ice, sediments, and soil. Mean limonene concentrations in two polluted Spanish rivers were 590 and 1600 ng/litre (Gomez-Belinchon et al., 1991). Samples of water collected from the Gulf of Mexico contained limonene at a concentration of 2-40 ng/litre (Sauer, 1981). Limonene has also been detected at Terra Nova Bay, Antarctica; water and pack ice samples contained limonene at concentrations up to 20 and 15 ng/litre, respectively (Desideri et al., 1991). Limonene concentrations up to 920 µg/g in soil and from 1 to 130 µg/litre in ground water were measured in a polluted area at a former site for the production of charcoal and pine tar products in Florida (McCreary et al., 1983). Limonene was also detected but not quantified in fish (i.e. carp) collected from Las Vegas Wash, Nevada (Hiatt, 1983).

ADDITIONAL EXAMPLE

7. In view of the limited available monitoring data, estimates of the fate and concentrations of methyl methacrylate in the Canadian environment were generated by a Level III fugacity model (Mackay & Paterson, 1981, 1982, 1991; Mackay et al., 1985) developed for southern Ontario, incorporating data on the physical and chemical properties of the chemical (Government of Canada, 1993), transformation half-lives (Howard et al., 1991), and proportion of production in the USA emitted to environmental media (see section 4) applied to the volume imported into Canada. Methyl methacrylate is not produced in Canada; approximately 22 000 t are imported (CPI, 1989). The model assumed emissions of 95% to air, 4.5% to water, and 0.5% to soil. The estimated relative proportions of methyl methacrylate predicted for air, water, soil, and sediment at steady state were 26.6%, 60.8%, 12.6%, and 0.03%, respectively. The amount of methyl methacrylate estimated to partition to fish was negligible. The relatively longer half-life for methyl methacrylate in water compared with air accounts for the higher estimated relative proportion predicted for the water compartment. Although such models are useful primarily for identification of the relative proportions of exposure from various media rather than for quantitative estimates of concentrations, the latter are presented here primarily as a baseline for comparison with measured concentrations. It should also be noted that such predicted values will vary in different countries depending upon production and releases of methyl methacrylate. The average concentrations estimated on the basis of the model were 2.44×10^{-4} µg/m³ in air, 0.13 ng/litre in surface water, 1.2×10^{-6} µg/g in soil, 8.7×10^{-8} µg/g in sediment, and 1.5×10^{-7} µg/g in fish (Government of Canada, 1993).

6.2 Human exposure

1. Exposure of the general population to 1,1,2,2-tetrachloroethane in environmental media may be estimated based on concentrations determined in various media and reference values for body weight and consumption patterns. Owing to the paucity of relevant data from other countries, particularly for recent years, exposure has been estimated here based primarily on data from North America, as an example. However, countries are encouraged to estimate total exposure on the basis of local data, possibly in a manner similar to that outlined here.

2. Mean levels in residential indoor air in Canada and the USA are generally below the limits of detection (i.e. <0.1 µg/m³; see Table 1). Based

Information on levels in source-dominated areas should also be included.

In cases (such as methyl methacrylate) where quantitative monitoring data are limited or are lacking entirely, concentrations of the chemical in environmental media predicted on the basis of modelling may be presented. However, the type of model and its limitations, as well as the assumptions and input data used in deriving the predicted concentrations, must be clearly outlined within the text

Section 6.2 provides a summary of the principal routes of human exposure and an estimate of the daily intake of the chemical by the general public and occupationally exposed individuals

For assessing potential exposure of the general public, this section should include data on levels in

on a daily inhalation volume for adults of 22 m³, a mean body weight for males and females of 64 kg, the assumption that 4 of 24 hours are spent outdoors (IPCS, 1994), and the range of mean levels of 1,1,2,2-tetrachloroethane in ambient air in recent surveys in Canada of <0.1-0.25 µg/m³, the mean intake of 1,1,2,2-tetrachloroethane from ambient air for the general population is estimated to range from <0.006 to 0.01 µg/kg body weight per day. Average intake of 1,1,2,2-tetrachloroethane from indoor air, based on the assumption that 20 of 24 hours are spent indoors (IPCS, 1994) and the mean concentration in residential indoor air in Canada and the USA of <0.1 µg/m³, is estimated to be <0.03 µg/kg body weight per day.

3. In a survey of 1159 household products in the USA, 1,1,2,2-tetrachloroethane was not detected above the limit of detection of 0.1% (see Table 1).

4. 1,1,2,2-Tetrachloroethane has not been detected in recent surveys of drinking-water in Canada and has been only extremely rarely detected (<0.03%) in recent surveys in the USA (detection limits 0.05-1.0 µg/litre; see Table 1), although it was detected in ground water near landfill sites in Finland at levels ranging from <0.1 to 2.5 µg/litre (Assmuth & Strandberg, 1993). Similarly, it has not been detected in three surveys of foodstuffs in Canada and the USA (detection limits were 1 µg/litre for liquids and 5-50 µg/kg for solids; see Table 1). No data were identified on levels of 1,1,2,2-tetrachloroethane in human breast milk. Drinking-water and food probably do not represent significant sources of exposure to 1,1,2,2-tetrachloroethane, based on its volatility and low potential for bioaccumulation.

5. Therefore, the principal media of exposure to 1,1,2,2-tetrachloroethane for the general population are likely indoor and outdoor air, with negligible amounts being contributed by food and drinking-water.

6. Although data on levels of 1,1,2,2-tetrachloroethane in the workplace were not identified, workers may be exposed to the substance via inhalation or dermal contact in "business services" (not further specified) as well as the chemical and allied products industries (ATSDR, 1994).

ADDITIONAL EXAMPLE

7. Adequate data on measured concentrations of methyl methacrylate in air, drinking-water, foodstuffs, and soil have not been identified; indeed, they are limited to non-detectable values in a limited number of small surveys. Although predicted concentrations in environmental media based on fugacity modelling are uncertain, they are helpful in estimating proportions of exposure from various media. Based on a daily inhalation volume for adults of 22 m³, a mean body weight for males and females of 64 kg, and a predicted concentration (by fugacity modelling; see section 6.1) of methyl methacrylate in ambient air in Canada of 2.44×10^{-4} µg/m³, the estimated intake of methyl methacrylate from air for the general population represents approximately 97% of the total intake from air, drinking-water, fish, and soil. Based on a daily volume of water consumption for adults of 1.4 litres, a mean body weight of 64 kg, and a predicted concentration of methyl methacrylate in surface water in Canada of 0.13 ng/litre (see section 6.1), the estimated intake of methyl methacrylate from drinking-water for the general population represents approximately 3.3% of total intake. Available data were inadequate to estimate the intake of methyl methacrylate from food, with the exception of intake from fish. Based on a

indoor air, drinking water, foodstuffs and consumer products.

Where available data are extensive, information from national surveys may be summarized in tabular format, with the general range of observed concentrations presented within the text.

In calculating the estimated daily intake (presented as mg/kg body weight per day) for the general public, the information and assumptions used in such calculations should be outlined.

Generally, estimated intakes are calculated only for adults; however, where considered appropriate, estimated intakes for other age groups (e.g., infants, children) may also be provided.

Estimated daily intakes for the general public derived from exposure modelling may also be included; however, the type of model and its limitations, as well as the relevant input data and assumptions used, must be clearly identified (see example on methyl methacrylate).

daily amount of fish ingested for adults of 23 g/day, a mean body weight for adults of 64 kg, and the predicted concentration of methyl methacrylate in fish in Canada of 1.5×10^7 $\mu\text{g/g}$ (see section 6.1), the estimated intake of methyl methacrylate from fish represents 0.06% of total intake. Based on a daily amount of soil ingested for adults of 20 mg, a mean body weight for adults of 64 kg, and a predicted concentration of methyl methacrylate in soil in Canada of 1.2×10^6 $\mu\text{g/g}$ (see section 6.1), the estimated intake of methyl methacrylate from soil, as a proportion of total intake, is negligible (0.0004%). Therefore, based on predicted concentrations in the Canadian environment, the overwhelmingly principal source of indirect exposure to methyl methacrylate for most of the general population is air.

9. Inhalation exposure to methyl methacrylate from the use of consumer products containing methyl methacrylate (e.g. dispersion paints and oil-based paints) was modelled using the US EPA Screening Consumers Inhalation Exposure Software (SCIES) computer model. All scenarios were based on the assumption that the percent composition of methyl methacrylate-based polymers in formulations of dispersion paints, varnishes, or lacquers is 15%, although residual monomer content is much less (European Union Draft Assessment on Methyl Methacrylate), and that 100% is absorbed. Although it has been reported that in some countries these products are not supplied to the general public, information on use patterns of these products in other countries was not available.

10. For the use of dispersion paints, the standard default values of the SCIES model were assumed for the following parameters: frequency of use, six events per year; mass of product, 13.6 kg; room size, 40 m^3 ; duration of use, 4.9 hours; house air exchange rate, 0.2 room air exchanges per hour; and user inhalation rate, 1.3 m^3/hour . The vapour pressure of methyl methacrylate was considered to be 38.4 torr (5.12 kPa) (Howard, 1989). Resulting estimated consumer exposure from inhalation was in the range of 10–100 mg/kg body weight per day. However, as the residual methyl methacrylate monomer content in dispersion paints is specified to be 0.1% (ECETOC, 1995), consumer exposure to methyl methacrylate would fall within the range of 10–100 $\mu\text{g/kg}$ body weight per day.

11. Occupations in which there is potential exposure to methyl methacrylate include those in the medical, dental, and beauty professions, such as chemical process operators, surgeons and surgical assistants, operating room nurses, dental technicians and hygienists, and beauty technicians applying synthetic fingernails (IARC, 1994). Exposure to methyl methacrylate in the workplace could be substantially greater than that in the general environment. Based on experience in the United Kingdom, for example, long-term personal exposures during monomer production average about 2 ppm (8.2 mg/m^3) and are less than 60 ppm (246 mg/m^3) (Cary et al., 1995). In open system industries such as cast sheet production, long-term exposures are higher, averaging 22.2 ppm (91 mg/m^3) and ranging from 0.5 to 165 ppm (2–677 mg/m^3). For various end uses of methyl methacrylate, including aerospace manufacture, plastics processing, and artificial teeth production, the mean long-term value for personal exposure was 13.4 ppm (55 mg/m^3), with a range of 0.8–109 ppm (3.3–447 mg/m^3). In medical and dental applications, peak concentrations up to 374 ppm (1533 mg/m^3) have been recorded, although short-term time-weighted-average exposures are likely to be less than 100 ppm (410 mg/m^3).

Estimated daily intakes (presented as mg/kg body weight per day) for occupationally exposed individuals may also be included; however, the data and assumptions used in such calculations should be outlined within the text.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

1. 1,1,2,2-Tetrachloroethane is readily absorbed following inhalation, ingestion, and dermal exposure and is likely distributed throughout the body, although relevant data are limited. Based on data on the metabolism of 1,1,2,2-tetrachloroethane in mice, Yllner (1971) suggested that the principal pathway of degradation involves stagewise hydrolytic cleavage of the carbon-chlorine bonds and oxidation to dichloroacetaldehyde hydrate, dichloroacetic acid (the major metabolite), and eventually glyoxylic acid. The glyoxylic acid is then metabolized to oxalic acid, glycine, formic acid, and carbon dioxide. A small proportion of the parent compound is probably non-enzymatically dehydrochlorinated to trichloroethylene, which is further converted to trichloroacetic acid and trichloroethanol. In addition, a minor amount of 1,1,2,2-tetrachloroethane may be oxidized to tetrachloroethylene, which, in turn, is metabolized to trichloroacetic acid and oxalic acid. It has also been proposed that 1,1,2,2-tetrachloroethane may be metabolized via cytochrome P-450 to dichloroacetyl chloride, which is hydrolysed to dichloroacetic acid (Halpert, 1982). In addition to the liver, metabolism may also occur in the epithelia of the respiratory tract and upper alimentary tract (Eriksson & Brittebo, 1991). The metabolites of 1,1,2,2-tetrachloroethane are eliminated in the urine, faeces, skin, and expired air.

Section 7 provides an overview of the kinetics and metabolism relevant to the assessment of human health hazards and risks.

Information on the extent of absorption, critical metabolic pathways (including principal metabolites), and elimination from studies in animals and where possible in humans, should be summarized briefly.

ADDITIONAL EXAMPLE

2. d-Limonene is rapidly distributed to different tissues in the body and is readily metabolized. Clearance from the blood was 1.1 litre/kg body weight per hour in males exposed for 2 hours to d-limonene at 450 mg/m³ (Falk Filipsson et al., 1993). A high oil/blood partition coefficient and a long half-life during the slow elimination phase suggest high affinity to adipose tissues (Falk et al., 1990; Falk Filipsson et al., 1993). In rats, the tissue distribution of radioactivity was initially high in the liver, kidneys, and blood after the oral administration of [¹⁴C]d-limonene (Igimi et al., 1974); however, negligible amounts of radioactivity were found after 48 hours. Differences between species regarding the renal disposition and protein binding of d-limonene have been observed. For rats, there is also a sex-related variation (Lehman-McKeeman et al., 1989; Webb et al., 1989). The concentration of d-limonene equivalents was about 3 times higher in male rats than in females, and about 40% was reversibly bound to the male rat specific protein, 2 μ -globulin (Lehman-McKeeman et al., 1989; Lehman-McKeeman & Caudill, 1992).

3. The biotransformation of d-limonene has been studied in many species, with several possible pathways of metabolism. Metabolic differences between species have been observed with respect to the metabolites present in both plasma and urine. About 25–30% of an oral dose of d-limonene in humans was found in urine as d-limonene-8,9-diol and its glucuronide; about 7–11% was eliminated as perillidic acid (4-(1-methylethenyl)-1-cyclohexene-1-carboxylic acid) and its metabolites (Smith et al., 1969; Kodama et al., 1976). d-Limonene-8,9-diol is probably formed via d-limonene-8,9-epoxide (Kodama et al., 1976; Watabe et al., 1981). In another study, perillidic acid was reported to be the principal metabolite in plasma in both rats and humans (Crowell et al., 1992). Other reported pathways of limonene metabolism involve ring hydroxylation and oxidation of the methyl group (Kodama et al., 1976).

Where possible, likely similarities or differences in the kinetics and metabolism of the chemical between humans and laboratory animals should be highlighted.

4. Following the inhalation exposure of volunteers to d-limonene at 450 mg/m³ for 2 hours, three phases of elimination were observed in the blood, with half-lives of about 3, 33, and 750 minutes, respectively (Falk Filipsson et al., 1993). About 1% of the amount taken up was eliminated unchanged in exhaled air, whereas about 0.003% was eliminated unchanged in the urine. When male volunteers were administered (per os) 1.6 g [¹⁴C]d-limonene, 50–80% of the radioactivity was eliminated in the urine within 2 days (Kodama et al., 1976). Limonene has been detected, but not quantified, in breast milk of non-occupationally exposed mothers (Pellizzari et al., 1982).

In cases where data are available from studies conducted with humans, a very brief outline of the experimental conditions should be presented.

ADDITIONAL EXAMPLE

5. Several physiologically-based pharmacokinetic (PBPK) models of 2-butoxyethanol absorption, metabolism, disposition, and excretion have been developed. One model examined human inhalation exposures during rest and exercise (Johanson et al., 1986; Johanson & Boman, 1991), while another (Shyr et al., 1993) addressed high-low dose and route of administration extrapolation based on animal data. In the Shyr et al. (1993) model, 2-butoxyethanol is metabolized to butoxyacetic acid and ethylene glycol. An additional model (Corley et al., 1994) combined aspects of the preceding models and addressed the disposition of butoxyacetic acid in rats and humans. The Corley et al. (1994) PBPK model describes the uptake, distribution, metabolism, and elimination of 2-butoxyethanol and its major metabolite, butoxyacetic acid. It was developed by expanding a previous inhalation model for 2-butoxyethanol (Johanson et al., 1986). The new model is comprised of two separate models for 2-butoxyethanol and butoxyacetic acid that are joined through metabolism in the liver. Both the 2-butoxyethanol and butoxyacetic acid models have the same eight compartments with an additional kidney compartment in the butoxyacetic acid model. Unlike the original model of Johanson et al. (1986), the muscle and skin compartments have been separated. Corley et al. (1994) have also incorporated protein binding and saturable elimination of butoxyacetic acid by the kidneys. Equations for additional routes of exposure (oral, dermal, and i.v. infusion) were also added. Physiological and biochemical parameters were allometrically scaled rather than using standard values for a 70-kg man. This allows simulations to be conducted for specific data sets. A rat version of the model was also developed.

Where related to the characterization of human health risks, information on physiologically-based pharmacokinetic (PBPK) models should include a brief summary of what the model describes, how it was developed and its limitations.

6. The model accurately predicted animal data at dose levels that did not cause haemolysis. At dose levels causing haemolysis, the model over predicted the amount of butoxyacetic acid excreted in the urine. This over prediction is assumed to be caused by toxicity in the kidneys that is secondary to haemolysis. The model does not accommodate toxicity in the kidneys and assumes that the kidneys will continue to function as normal, thus leading to the over prediction of butoxyacetic acid in the urine. The Corley et al. (1994) model was able to accurately predict the Johanson and Boman (1991) human whole body exposure blood data when it was assumed that the sampled blood did not represent systemic venous blood, but instead represented venous blood draining from the skin compartment. This blood had not yet been diluted by the venous blood pool. Using this approach, Corley et al. (1994) suggested that dermal uptake contributes 21% of total uptake of 2-butoxyethanol in whole body exposures, rather than the 75% suggested by Johanson and Boman (1991).

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

As the data base and the relative importance of different findings varies widely between different chemicals, there is flexibility in the structure of this section: in specific instances approaches other than the present format will be more appropriate

Normally studies on laboratory mammals are described in this section. However, studies on all species that are relevant to human health assessment are included.

In cases of exceptional complexity of a section in Chapter 8, a summary paragraph may be included at the end of such a subsection.

In general, the section should be subdivided as follows: single exposure, short-term exposure, medium-term exposure, long-term exposure/ carcinogenicity. Single exposure generally should cover exposure up to 24 hours, short-term exposure up to 28 days, and medium-term exposure up to 50% of the life span, (for example, 90-day studies).

Section 8.1 provides a brief overview of the acute toxicity (low, moderate or high) following inhalation, ingestion and dermal exposure.

Where data are extensive, only ranges of LC₅₀s and LD₅₀s for inhalation, ingestion and dermal exposure for major laboratory species should be presented.

A brief summary of critical acute effects may also be presented.

8.1 Single exposure

1. The acute toxicity of 1,1,2,2-tetrachloroethane in experimental animals is slight to moderate. Exposure to concentrations of around 1000 ppm (6980 mg/m³) for 4 or 6 hours or about 5000–6000 ppm (34 900–41 880 mg/m³) (duration not specified) caused deaths in rats and mice, respectively. Oral LD₅₀s of 250–330 and 1000 mg/kg body weight for 1,1,2,2-tetrachloroethane in rats have been reported. The dermal LD₅₀ (24 hours) in rabbits was 6360 mg/kg body weight (Kennedy & Graepel, 1991; ATSDR, 1994).

ADDITIONAL EXAMPLE

2. o-Toluidine is harmful following acute oral exposure (LD₅₀s of 900 and 940 mg/kg body weight in rats) and is of low acute toxicity following dermal exposure (LD₅₀ of 3235 mg/kg body weight in rabbits) (Smyth et al., 1962; Jacobson, 1972). Acute effects include cyanosis, increased methaemoglobin levels, and related effects in the spleen. Useful data on effects associated with inhalation exposure were not identified.

8.2 Short-term exposure

4. In general, dose–response relationships have not been well characterized in available short-term studies in experimental animals owing to limitations of the studies, including use of only one level of exposure or inadequate description of protocol or results. Hepatic effects, including increased organ weight, congestion, fatty degeneration, histological changes, alterations in levels of enzymes, and elevated DNA synthesis (the degree of which increased with dose), have been observed in rodents following short-term inhalation of 1,1,2,2-tetrachloroethane at concentrations as low as 13.3 mg/m³ (for 2–10 days) and ingestion of the chemical at doses as low as 75 mg/kg body weight per day (for 4 days) in the few available, principally limited, studies (Horiuchi et al., 1962; Gohlke & Schmidt, 1972; Schmidt et al., 1972; Hanley et al., 1988; NTP, 1996). In a limited account of a study in rats, Ulanova et al. (1984) reported effects on the nervous system and kidneys to be similar following continuous or intermittent exposure for 4–27 days to comparable time-weighted-average concentrations of 1,1,2,2-tetrachloroethane (235 and 250 mg/m³).

The extent of the presentations in Sections 8.2 Short-term exposure, Section 8.3 Medium-term exposure, and 8.4 Long-term exposure and carcinogenicity depends primarily upon selection of the critical end-point(s) related to the assessment of human health and environmental effects, and the available dataset.

In cases where critical information for hazard identification and risk characterization is derived from medium-term and/or long-term studies, Section 8.2 provides only a brief overview of the effects and related effect levels derived from experimental toxicity studies of up to approximately 28 days duration.

8.3 Medium-term exposure

1. Only a few limited studies have been identified on the effects in experimental animals following subchronic exposure to 1,1,2,2-tetrachloroethane (see Table 3). Ingestion of up to 316 mg/kg body weight per day had no effects on body weight gain or mortality in groups of five male or female B6C3F₁ mice, whereas doses of 100 (females) or 178 (males) mg/kg body weight per day and above resulted in decreased body weight gain in groups of five male or female Osborne-Mendel rats in subchronic studies preliminary to longer-term bioassays (no other end-points appear to have been examined) (NCI, 1978). Histopathological damage (including chronic inflammation, necrosis, or atrophy) was observed in the liver, kidney, testicles, and thyroid gland of rats ($n = 10$ per group) administered oral 1,1,2,2-tetrachloroethane doses of 3.2–50 mg/kg body weight per day for periods ranging from 2 to 150 days (Gohlke et al., 1977), although the limited documentation of results in this study precludes validation of an effect level.

In cases (such as 1,1,2,2-tetrachloroethane) where critical data are derived from long-term studies, the protocols and results of medium-term studies may be summarized (along with other long-term investigations) in tabular format (for example, see Table 3 at the end of this annex), with only a brief overview of the more relevant findings and effect levels summarized within the text.

2. Exposure to 1,1,2,2-tetrachloroethane at 50 mg/m³ for approximately 5 weeks resulted in alterations in biochemical parameters and organ weights in male rats (strain and number not specified), although no “morphological changes” were noted upon examination (the nature and extent of the histopathological examination were unspecified) (Schmidt et al., 1975). Hepatic effects, including a transient increase in DNA synthesis, reversible histopathological changes (cytoplasmic vacuolization and hyperplasia), and an increase in relative liver weight, were observed in female Sprague-Dawley rats ($n = 55$) exposed for 15 weeks to 560 ml/m³ (reported by ATSDR [1994] to be equivalent to 130 ppm [907 mg/m³], although infor-

In cases (such as limonene) in which effects observed in a medium-term study are considered to represent the critical end-point (and the dataset is more limited), the level of detail in the description of the key study is enhanced, including where

mation on the exposure level presented in the original paper was unclear) (Truffert et al., 1977).

ADDITIONAL EXAMPLE

3. Peroral administration of d-limonene to rats at a dose of 400 mg/kg body weight for 30 days resulted in a 20–30% increase in the amount and activity of different liver enzymes (cytochrome P-450, cytochrome b5, aminopyrine demethylase, and aniline hydroxylase), increased relative liver weight, and decreased cholesterol levels (Ariyoshi et al., 1975). Administration of d-limonene (0, 2, 5, 10, 30, and 75 mg/kg body weight per day) by gavage to groups of 10 male rats, 5 days/week for 13 weeks (Webb et al., 1989), resulted in the pathological formation of granular casts at the outer zone of the renal medulla. The no-observed-effect level (NOEL), based upon histological examination of the kidneys, was considered to be 5 mg/kg body weight per day. The LOEL for increased liver and kidney weight was 75 mg/kg body weight per day, the highest dose tested. The NOEL for effects in the liver was 10 mg/kg body weight; the no-observed-adverse-effect level (NOAEL) for effects in the liver was 30 mg/kg body weight per day. Linear regression analysis revealed a dose-related trend in the increased relative weights of the kidney and liver at 30 and 75 mg/kg body weight per day. No histopathological changes were observed in the liver in these two studies. The amount and activity of different liver enzymes were not investigated, and thus the increase in relative liver weight may be due to enzyme induction.

8.4 Long-term exposure and carcinogenicity

4. The chronic toxicity of 1,1,2,2-tetrachloroethane has not been extensively investigated; available studies are not adequate to allow the confident determination of an “effect level” for non-neoplastic effects. A reversible decrease in body weight and a reversible increase in lipid content of the liver were observed in male rats exposed to 1,1,2,2-tetrachloroethane by inhalation at 13.3 mg/m³ for 110 or 265 days or for 265 days with a 60-day recovery period (seven rats were killed at each interval); there were also reversible alterations in haematological parameters, which were statistically significantly different from controls only at one point in time during the study, and increased adrenocorticotrophic hormone activity in the hypophysis (Schmidt et al., 1972). However, histopathological effects were not described in the published account of the investigation. In a study for which only secondary accounts were available, early signs of liver degeneration were observed in rabbits exposed to 100 mg/m³ for 7–11 months (Navrotsky et al., 1971) (no further details were provided).

5. An increase in the incidence of hepatocellular carcinomas was observed in groups of 50 ($n = 20$ in controls) male and female B6C3F₁ mice administered technical-grade 1,1,2,2-tetrachloroethane in corn oil by gavage at time-weighted-average daily doses of 142 or 284 mg/kg body weight for 78 weeks (1/18, 13/50, and 44/49 in males, and 0/20, 30/48, and 43/47 in females, in the vehicle controls, low-dose group, and high-dose group, respectively). These tumours also appeared earlier in mice administered the higher dose. Slightly decreased body weight gain and increased mortality were also observed in exposed mice; there were no increases in the incidences of non-neoplastic lesions (NCI, 1978).

6. There were no significant increases in the incidence of any type of neoplastic or non-neoplastic lesion in groups of 50 ($n = 20$ in controls) male or female Osborne-Mendel rats similarly administered technical-grade

appropriate, size of experimental and control groups, species and strain, dosing regime, including hours/days, days/week for designated period of exposure, route and vehicle of exposure, end-points examined at what periods of observation after dosing, results (i.e., incidence) for all important biological end-points examined including assessment of exposure-response relationships and statistical analysis.

In cases where the critical end-point(s) is derived from long-term exposure and/or carcinogenicity bioassays, the type and extent of the presentation will depend upon the available dataset.

For the example of 1,1,2,2-tetrachloroethane, data on the carcinogenic effects considered the critical end-point for human health hazard identification and risk assessment, are presented in detail within the text; the description, including information on size of experimental and control groups, species and strain, dosing regime, including hours/days, days/week for designated period of exposure, route and vehicle of exposure, end-points examined at what periods of observation after dosing, results (i.e.,

1,1,2,2-tetrachloroethane in corn oil by gavage at time-weighted-average doses of 62 or 108 mg/kg body weight per day (males) and 43 or 76 mg/kg body weight per day (females) for 78 weeks, although there were two males with hepatocellular carcinomas and one with a hepatic neoplastic nodule in the high-dose group. There were also reversible dose-related decreases in body weight gain and increased mortality in exposed rats (NCI, 1978).

7. In a limited bioassay designed to investigate the potential of 1,1,2,2-tetrachloroethane to induce pulmonary adenomas in a sensitive strain of mice, there was no increase in the number of these tumours in a group of 20 strain A mice intraperitoneally administered the chemical for 24 weeks; however, mortality was high in this study (Theiss et al., 1977; Stoner, 1991).

8. In an initiation/promotion assay, 1,1,2,2-tetrachloroethane did not initiate formation of α -glutamyltranspeptidase-positive foci in the liver (a putative preneoplastic indicator) in groups of 10 male Osborne-Mendel rats administered an oral dose of 100 mg/kg body weight followed by exposure to phenobarbital for 7 weeks, although it acted as a potent promoter in rats initiated with a single dose of diethylnitrosamine followed by exposure to 1,1,2,2-tetrachloroethane by gavage for 7 weeks at 100 mg/kg body weight per day (Story et al., 1986; Milman et al., 1988).

9. Little information on the mechanism(s) of liver tumour induction in mice exposed to 1,1,2,2-tetrachloroethane has been identified. Several of the metabolites of 1,1,2,2-tetrachloroethane, including trichloroethylene, tetrachloroethylene, trichloroacetic acid, and dichloroacetic acid, have been hepatocarcinogenic in experimental animals (e.g. NCI, 1977; Maltoni et al., 1986, 1988; NTP, 1986, 1990; Herren-Freund et al., 1987; Bull et al., 1990; DeAngelo et al., 1991). Indeed, the toxicological profile for 1,1,2,2-tetrachloroethane is very similar to that for dichloroacetic acid, the principal metabolite.

ADDITIONAL EXAMPLE [1,2-DICHLOROETHANE]

10. Little information was presented on non-neoplastic effects in available chronic studies. Changes in serum parameters indicative of liver and kidney toxicity were observed in groups of 8–10 male or female Sprague-Dawley rats exposed to airborne concentrations as low as 202 mg/m³ for 12 months, although histopathological examinations were not conducted in this study (Spreafico et al., 1980).

11. The carcinogenicity of 1,2-dichloroethane has been investigated in a few limited bioassays in experimental animals (limitations include short duration of exposure and high mortality). In an inhalation study, no significant increase in the incidence of any type of tumour was reported in groups of 90 male or female Sprague-Dawley rats exposed to concentrations of 1,2-dichloroethane up to 150 ppm (607 mg/m³), 7 hours/day, 5 days/week, for 78 weeks and observed until spontaneous death (Maltoni et al., 1980). However, mortality was high in this study, although it was not related to concentration, and incidence rates were not adjusted for differential mortality among groups. There was a non-significant increase in the incidence of mammary gland adenomas and fibroadenomas in female Sprague-Dawley rats (n = 50) exposed to 1,2-dichloroethane at 50 ppm (200 mg/m³), 7 hours/day, 5 days/week, for 2 years in an assay in which no other compound-related toxicity was observed (Cheever et al., 1990). No increase in the incidence of any type of tumour was observed in groups of 90 male or female Swiss mice exposed to concentrations of 1,2-dichloroethane up to 150 ppm (607 mg/m³), 7 hours/day, 5 days/week, for 78 weeks and

incidence) for all neoplastic end-points examined, including assessment of exposure-response relationships and statistical analysis. Results of non-critical effect levels are presented in a tabular format (see Table 3 at the end of this annex), and only briefly summarized in the text.

Actual (tumour) incidence data should be presented in text and/or tables, rather than simply the percentage of animals affected.

Information from more limited carcinogenicity bioassays is only briefly summarized within the text.

For the example of 1,2-dichloroethane, where there are a limited number of important studies, data critical for the hazard identification and risk characterization (in this case on carcinogenicity) are detailed within the text. Information on size of experimental and control groups, species and strain, dosing regime, including hours/days, days/week for designated period of exposure, route and vehicle of exposure, end-points examined at what periods of observation after dosing, results (i.e., incidence) for all neoplastic end-points examined including assessment of exposure-response relationships and statistical analysis, should

observed until spontaneous death (Maltoni et al., 1980).

12. In contrast, there has been convincing evidence of increases in tumour incidence in two species following ingestion. There were significant increases in the incidence of tumours at several sites in Osborne-Mendel rats (n = 50 of each sex in exposed groups; n = 20 matched controls; n = 60 pooled controls) administered time-weighted-average doses of 47 or 95 mg/kg body weight per day in corn oil by gavage, 5 days/week, for 78 weeks, followed by 32 weeks of observation. The incidence of squamous cell carcinomas of the stomach was significantly increased in both groups of exposed males (0/60, 0/20, 3/50, and 9/50 in pooled [from concurrent studies] vehicle controls, matched vehicle controls, low-dose group, and high-dose group, respectively). There were also significant increases in the incidence of haemangiosarcomas in exposed males (1/60, 0/20, 9/50, and 7/50) and females (0/59, 0/20, 4/50, and 4/50). The incidence of fibromas of the subcutaneous tissue was significantly increased in exposed males (0/60, 0/20, 5/50, and 6/50). In females, there were significant increases in the incidences of adenocarcinomas and fibroadenomas (combined) of the mammary gland (6/59, 0/20, 15/50, and 24/50). Mortality was significantly higher in both males and females in the high-dose group, and there was a greater frequency of clinical signs of toxicity in exposed rats compared with controls. Chronic murine pneumonia was present in 60–94% of rats in each group, although the incidence was not related to dose (NCI, 1978).

13. The incidence of lung tumours (benign lung papillomas) was significantly increased in female non-inbred Ha:ICR mice (n = 30) following repeated dermal application of 1,2-dichloroethane, 3 times/week, for 440–594 days (van Duuren et al., 1979). Repeated intraperitoneal injections of 1,2-dichloroethane resulted in a dose-related increase in the number of pulmonary adenomas per mouse in a screening bioassay in a susceptible strain (A/St), although none of these increases was significant (Theiss et al., 1977). Concomitant exposure to inhaled 1,2-dichloroethane and disulfiram in the diet resulted in an increased incidence of intrahepatic bile duct cholangiomas and cysts, subcutaneous fibromas, hepatic neoplastic nodules, interstitial cell tumours in the testes, and mammary adenocarcinomas in rats, compared with rats administered either compound alone or untreated controls (Cheever et al., 1990). No potential to initiate or promote tumour development was evident in three bioassays (van Duuren et al., 1979; Klaunig et al., 1986; Story et al., 1986; Milman et al., 1988), although the extent of histopathological examination was limited in these studies.

ADDITIONAL EXAMPLE

14. In the few studies identified in which the chronic toxicity and carcinogenicity of methyl methacrylate were investigated, the observed effects were, in general, similar to those reported in short-term and subchronic studies and included inflammation and epithelial hyperplasia of the nasal cavity and degeneration of the olfactory sensory epithelium. Based on the results of a well documented inhalation study in F344/N rats and B6C3F₁ mice reported by the NTP (1986) and Chan et al. (1988), there was no evidence of carcinogenicity of methyl methacrylate for groups of 50 male F344/N rats and 50 male and 50 female B6C3F₁ mice exposed to 500 or 1000 ppm (2050 or 4100 mg/m³) and groups of 50 female rats exposed to 250 or 500 ppm (1025 or 2050 mg/m³) for 2 years. Based on inflammation and degeneration of the olfactory epithelium in the nasal cavity (accompanied by variable atrophy of the nerve bundles in the submucosa

be presented to permit adequate assessment and interpretation of the studies and their results.

Information from assays providing less additional weight to the overall evidence for carcinogenicity than standard carcinogenicity bioassays, are only briefly summarized within the text.

In cases where non-neoplastic effects are considered to be the critical end-points (such as for methyl methacrylate having a moderately-sized dataset), the protocols and results of relevant studies may be summarized in tabular format, with descriptions of the critical studies and end-points presented within the text. The key study/ies and the basis and selection of

and, in the most severely affected areas, replacement of sensory neuroepithelial cells with respiratory epithelium) and minimal increases in the numbers of alveolar macrophages in the nasal cavity at all dose levels, the LOEL in rats was considered to be 250 ppm (1025 mg/m³). In mice, the LOEL was considered to be 500 ppm (2050 mg/m³) on the basis of lower mean body weights in exposed animals and localized histopathological effects at the site of entry (including inflammation and degeneration of the olfactory epithelium).

the critical end-point(s) and identification of no-observed-(adverse)-effect levels [NO(A)ELs], lowest-observed-(adverse)-effect levels [LO(A)ELs] or benchmark doses should be clearly outlined within the text. It is not necessary to report further NOAEL/LOAEL values for other individual studies. They should be presented for potentially critical effects related to repeated-dose toxicity.

8.5 Genotoxicity and related end-points

1. Results of identified *in vitro* studies are summarized in Table 4. Predominantly negative results have been reported for the induction of gene mutation in prokaryotic systems with and without metabolic activation, whereas both positive and negative results have been observed for gene conversions in yeast and fungi. 1,1,2,2-Tetrachloroethane induced sister chromatid exchange but not chromosomal aberrations, DNA repair, or unscheduled synthesis of DNA in mammalian cells *in vitro*.
2. Exposure to 1,1,2,2-tetrachloroethane at 349 mg/m³ for 5 days did not induce dominant lethal mutations in rats, and results for chromosomal aberrations in rat bone marrow cells were equivocal; however, this concentration did not induce cytotoxicity (McGregor, 1980). 1,1,2,2-Tetrachloroethane did not induce unscheduled DNA synthesis in hepatocytes of mice exposed to doses of up to 1000 mg/kg body weight by gavage, whereas results for the induction of S-phase synthesis were negative and equivocal (Mirsalis et al., 1989).
3. 1,1,2,2-Tetrachloroethane has also been reported to bind to cellular macromolecules, including DNA, RNA, and proteins of several organs in rodents, following *in vivo* exposure (Mitoma et al., 1985; Colacci et al., 1987; Eriksson & Brittebo, 1991). Results for cell transformation in mammalian cells have been mixed, with positive results being reported by only one of four investigators (Little, 1983; Tu et al., 1985; Milman et al., 1988; Colacci et al., 1990, 1992, 1993).
4. 1,1,2,2-Tetrachloroethane did not induce sex-linked recessive lethal mutations or mitotic recombination in *Drosophila melanogaster* in three studies (McGregor, 1980; Woodruff et al., 1985; Vogel & Nivard, 1993).
5. With the possible exception of the equivocal results for chromosomal aberrations observed in female rats following inhalation (McGregor, 1980), the weight of evidence overall indicates that 1,1,2,2-tetrachloroethane is not genotoxic or that it is only weakly genotoxic, acting through a mechanism that results in gene conversion and induction of sister chromatid exchange.

*Summary only of data on genotoxicity and related end-points is presented; for individual studies, the reader is referred to the source document. Only when it is relevant, are highest effective or lowest ineffective concentration dose levels given. Data are presented in phylogenetic order by end point, separated in sections on studies *in vitro* and *in vivo*. When extensive new data have become available since the preparation of the source document, data on genotoxicity may be presented in table form in an appendix.*

This section should also include a summary of the weight of evidence concerning the genotoxic potential of the chemical.

ADDITIONAL EXAMPLE

6. On the basis of available data, there is no evidence that d-limonene or its metabolites are genotoxic or mutagenic. Limonene and its epoxides

were not mutagenic when tested at concentrations of 0.3–3333 µg/plate in *in vitro* assays using different strains of *Salmonella typhimurium*, in the presence or absence of metabolic activation (Florin et al., 1980; Watabe et al., 1981; Haworth et al., 1983; Connor et al., 1985; NTP, 1990). *d*-Limonene did not increase the frequency of forward mutation at the TK+/ locus in mouse L5178Y cells (NTP, 1990), induce cytogenetic damage in Chinese hamster ovary cells (Anderson et al., 1990), or malignantly transform Syrian hamster embryo cells (Pienta, 1980). In one *in vitro* study, following exposure with benzo(a)pyrene, *d*-limonene (21.9 µmol/litre) inhibited the formation of transformed cell colonies in tracheal epithelium isolated from rats (Steele et al., 1990).

7. No evidence of mutagenicity was reported in an *in vivo* spot test with mice, involving the intraperitoneal injection of limonene at 215 mg/kg body weight per day on days 9–11 during gestation (Fahrig, 1984).

8.6 Reproductive toxicity

8.6.1 Effects on fertility

In a valid 2-generation study with groups of 24 female and 12 male Sprague-Dawley rats carried out by Angerhofer (1985), 4-nitrophenol dissolved in ethanol was applied dermally at doses of 0, 50, 100 or 250 mg/kg bw per day on 5 days per week. The F₀ generation was exposed over a period of 140 days before mating. Dosing of the F₀ females continued throughout breeding, gestation and lactation. Groups of 26 females and 13 males of the F₁ generation were then exposed for 168 days in the same manner as had been the F₀ rats; the females were again exposed throughout breeding, gestation and lactation. Apart from dose-related signs of skin irritation (erythema, scaling, scabbing and cracking) in dosed animals, the gross and histopathological examination provided no indication of significant adverse effects. The calculated indices concerning fertility, gestation, viability and lactation were not different from those of controls. The testis to body weight ratios in the F₀ generation were not affected, and histological lesions were not observed in the testes. In a 28-day study in rats (See 8.3.1), testicular atrophy and inhibition of spermatogenesis were observed in some animals after oral dosing at a level of 630 mg/kg, but not at 210 mg/kg.

8.6.2 Developmental toxicity

2-Nitrophenol

In a range-finding study with Charles River COBS[®] CD[®] rats (5 dams/group; application of 0, 50, 125, 250, 500 or 1,000 mg/kg via gavage from day 6 to 15 of gestation; uterine examination on day 20), a dose-level of ≥ 500 mg/kg caused signs of maternal toxicity (transient, but dose-related decrease in weight gain early during treatment). One high-dosed animal died, but no cause of death could be determined. Other clinical findings included darkly coloured urine at concentrations ≥ 250 mg/kg and yellow staining of haircoat (at the nose, mouth, anogenital area) at ≥ 125 mg/kg, while the necropsy findings gave no biologically meaningful differences in surviving dams. At the highest dose-level of 1,000 mg/kg, a slight but statistically significant (also compared to historical controls) increase in group mean postimplantation losses (13.8 % versus 8.2 in controls) and mean early resorptions (2.3 versus 1.2 in controls) was seen. No effects were observed on the number of viable fetuses, implantations or corpora lutea (International Research and Developmental Corporation, 1983).

Descriptions of in vivo genotoxicity studies (whether in a table or within the text) should include the species and exposure conditions.

The section is divided, where data are available, in subsections

8.6.1 Effects on fertility

8.6.2 Developmental toxicity

In cases, in which such effects are not considered critical for the overall hazard identification and risk characterization, the results of the studies may be summarized within the text (including a brief description of the exposure conditions).

Where reproductive toxicity is observed and existing data allow, NOAEL (or LOAEL) values for reproductive effects should be given for the key studies. Developmental effects should be mentioned within the context of exposure levels associated with maternal toxicity. In cases where reproductive or developmental effects are considered critical endpoints for human health

4-Nitrophenol

In both studies cited below, a complete examination of the pups for possible teratogenic effects was not performed. In addition, due to limitations of these studies (i.e. use of only one dose group or exposure to a mixture), reliable NO(A)EL values cannot be derived.

In a study performed by Booth et al. (1983) groups of 50 female CD-1 mice received daily oral doses of 400 mg/kg bw 4-nitrophenol via gavage from day 7 to 14 of gestation. The survival rate in pregnant mice (n = 36) was 81 % versus 100 % in controls and dosed animals showed less maternal weight gain. No changes were observed in the reproductive index (ratio between survivors delivered and pregnant survivors). The average number of live pups per litter was slightly decreased, but 4-nitrophenol produced no gross abnormalities.

Kavlock (1990) studied the developmental toxicity of 4-nitrophenol in Sprague-Dawley rats. The substance (dissolved in a mixture of water, Tween 20, propylene glycol and ethanol [4:4:1:1]) was applied via gavage to groups of 12 - 13 animals at doses of 0, 100, 333, 667 or 1 000 mg/kg bw on day 11 of gestation. Endpoints concerning maternal toxicity included signs of toxicity, mortality, body weight gain and the number of implantation scars in the uteri at weaning. In the offspring viability, body weight on postnatal days 1 - 6, overt malformations and perinatal loss were recorded. In dams the mortality was increased at a dose level of ≥ 667 mg/kg bw and at a dose level of ≥ 333 mg/kg bw the litter size on postnatal days 1 and 6 was non significantly decreased.

8.7 Other toxicity

1. Epidermal and dermal changes were reported in rabbits following cutaneous exposure to 1,1,2,2-tetrachloroethane (Smyth et al., 1969). Exposure to 580 ppm (4050 mg/m³) 1,1,2,2-tetrachloroethane caused ocular irritation in guinea-pigs (Price et al., 1978). No information on the sensitization potential of this substance was identified.

2. Immunological effects have been observed in limited studies in rabbits exposed to 1,1,2,2-tetrachloroethane by inhalation. For example, Shmutter (1977) reported a decrease in the titres of typhoid antibodies, an increase in the electrophoretic mobility of antibodies towards - and - globulin fractions, and a decrease in the level of "normal" haemolysins to the Forsman's antigen of sheep erythrocytes in animals exposed to 1,1,2,2-tetrachloroethane at 10 mg/m³ and above for 8 months.

3. Neurological effects have been observed in several species following acute or short-term exposure to 1,1,2,2-tetrachloroethane (e.g. at concentrations as low as 200 ppm [1396 mg/m³] for 6 hours [Horvath & Frantik, 1973] or 50 mg/m³ for approximately 5 weeks [Schmidt et al., 1975]). A single oral dose of 50 mg/kg body weight increased levels of several neurotransmitters in the brain of rats (Kanada et al., 1994).

hazard identification, appropriate additional details on experimental design and end-points examined should be presented.

Specific areas may be added as necessary if the information for the chemical warrants this: For example: dermal and ocular irritation, dermal and respiratory sensitisation, immunotoxicity or neurotoxicity.

ADDITIONAL EXAMPLE

8.8 Mode of action

24. The mechanisms by which formaldehyde induces tumours in the

The final subsection should cover "Mode of action" but

respiratory tract of rats are not fully understood. Inhibition of mucociliary clearance is observed in rats exposed acutely to concentrations of formaldehyde greater than 2.4 mg/m³ (Morgan *et al.*, 1986a). There is also evidence that glutathione-mediated detoxification of formaldehyde within nasal tissues becomes saturated in rats at inhalation exposures above 4 ppm (4.8 mg/m³) (Casanova and Heck, 1987). This correlates with the non-linear increase in DNA–protein crosslink formation at exposures above this level

25. A sustained increase in nasal epithelial cell regenerative proliferation resulting from cytotoxicity and mutation, for which DNA–protein crosslinks serve as markers of potential, have been identified as likely, although not sufficient, factors contributing to the induction of nasal tumours in rats induced by formaldehyde. This hypothesis is based primarily on observation of consistent, non-linear dose–response relationships for all three endpoints (DPX, sustained increases in proliferation and tumours) and concordance of incidence of these effects across regions of the nasal passages (see Table 6).

26. Increased cellular proliferation as a consequence of epithelial cell toxicity is the most significant determinant of neoplastic progression. The effect of formaldehyde exposure on cell proliferation within the respiratory epithelium of rats has been examined in a number of short-term, subchronic and chronic studies (Swenberg *et al.*, 1983; Wilmer *et al.*, 1987, 1989; Zwart *et al.*, 1988; Reuzel *et al.*, 1990; Monticello *et al.*, 1991, 1996; Casanova *et al.*, 1994). A sustained increase in proliferation of nasal epithelial cells has not been observed following the exposure of rats to concentrations of formaldehyde of ≤ 2.4 mg/m³ (2 ppm) irrespective of the exposure period. In rats exposed to formaldehyde, increased respiratory epithelial cell proliferation in the nasal cavity was more closely related to the concentration to which the animals were exposed than to the total cumulative dose (Swenberg *et al.*, 1983). The relative magnitude of increase in proliferative response is dependent upon the specific site within the nasal cavity and not always directly related to the length of exposure (Swenberg *et al.*, 1986; Monticello *et al.*, 1991, 1996; Monticello and Morgan, 1994). The extent of the carcinogenic response following exposure to formaldehyde is also dependent upon the size of the target cell population within specific regions of the nasal cavity (Monticello *et al.*, 1996).

27. Although direct evidence in humans is lacking, increased epithelial cell proliferation (respiratory and olfactory epithelia) and DNA–protein crosslink formation (middle turbinates, lateral wall and septum and nasopharynx) within the upper respiratory tract have been observed in monkeys exposed to formaldehyde by inhalation (Monticello *et al.*, 1989; Casanova *et al.*, 1991). At similar levels of exposure, concentrations of DNA–protein crosslinks were approximately an order of magnitude less in monkeys than in rats. In rats, the cumulative yield of DNA–protein crosslinks was similar after acute and subchronic exposure, suggesting rapid repair (Casanova *et al.*, 1994). Using a model system in which rat trachea populated with human tracheobronchial epithelial cells were xenotransplanted into athymic mice, Ura *et al.* (1989) reported increased human epithelial cell proliferation following *in situ* exposure to formaldehyde.

only if sufficient relevant information is available and this assists in the risk characterisation.

In cases, where such data are not considered critical to human risk assessment, the results can be summarized in sections 8.1 - 8.7.

9. EFFECTS ON HUMANS

1. Death has been reported following suicidal ingestion of doses of 1,1,2,2-tetrachloroethane estimated to range from 285 to 6000 mg/kg body weight (ATSDR, 1994). Hepatic effects and death have also been reported following accidental poisoning with 1,1,2,2-tetrachloroethane. Other effects noted in earlier reports of workers or volunteers exposed to 1,1,2,2-tetrachloroethane concentrations ranging up to 1800 mg/m³ include respiratory failure, mucosal irritation, unconsciousness, gastrointestinal and neurological distress, jaundice, liver enlargement or degeneration, headache, tremors, dizziness, numbness, and drowsiness (ATSDR, 1994).

2. No statistically significant increase in mortality due to any specific cause was noted in a limited epidemiological investigation in a population of 1099 men exposed to unknown concentrations of "tetrachloroethane" (Norman et al., 1981). The prevalence of nervous symptoms, including tremors, headaches, and vertigo, was reported to increase with airborne concentration of 1,1,2,2-tetrachloroethane (up to 98 ppm [684 mg/m³]) in a group of 380 workers in India exposed for varying durations, although no information was presented on the prevalence of these signs in an unexposed group. Exposed workers also reported loss of appetite, nausea, vomiting, and abdominal pain (Lobo-Mendonca, 1963). Similar symptoms (i.e. loss of appetite, bad taste in the mouth, epigastric pain, sensation of pressure in the liver area, headaches, general debility, lack of stamina, loss of body weight, and occasional painful prurigo) were observed in employees of a penicillin plant exposed to concentrations of 1,1,2,2-tetrachloroethane ranging from 10 to 1700 mg/m³. The prevalence of symptoms decreased with the implementation of improvements in working conditions, and most workers were reported to be free of symptoms when maximum levels were below 250 mg/m³ (Jeney et al., 1957).

ADDITIONAL EXAMPLE

3. Protocols and results of cross-sectional studies in which respiratory effects of methyl methacrylate have been investigated in occupationally exposed populations are presented in Table 3. For example, in a study in which smoking was taken into account, an increase in the prevalence of chronic cough (as evaluated by questionnaire) was observed in a small group of workers ($n = 40$) exposed exclusively to methyl methacrylate for at least 5 years in two factories (mean atmospheric levels of methyl methacrylate in the two factories were 18.5 and 21.6 ppm [75.8 and 88.6 mg/m³]) compared with controls engaged in similar job categories, but without exposure to methyl methacrylate (Marez et al., 1993). Spirometric values did not differ

The structure and subheadings in this section depend on the data available. Division into subsections is only needed when it increases the readability of the section

Information from case reports is often the first indication of an adverse health effect. However, it is not usually possible to draw causal inferences from such reports. In general, a very brief summary of such reports is sufficient. Emphasis should be on studies relevant to the hazard characterization and dose-response analyses.

Studies on exposed volunteers may be used for hazard identification and dose-response analysis. However, almost always they are limited to short-term exposure and short-term follow-up. In general, a very brief summary of such reports is sufficient.

Cross-sectional studies (e.g., reports on clinical findings among exposed populations, or on biomarkers of exposure/effect) often lack proper epidemiological design and long-term exposure assessment and are therefore difficult to interpret. In general, a brief summary of such reports is sufficient.

The extent of the presentation of epidemiological data is dependent on its contribution to hazard identification and dose-response analysis.

before the work shift, but two of nine parameters decreased during the work shift. Information concerning exposure to other respiratory irritants was not provided; although increased cough and mild airway resistance correlated with exposure to methyl methacrylate, peak versus mean exposures were not examined. In other studies in which there was some quantitative information on exposure, results have varied, with effects on respiratory function being observed in some cases at mean concentrations as low as 11 mg/m³ (Jedrychowski, 1982) and no effects in other investigations at time-weighted-average concentrations up to 40–50 ppm (164–205 mg/m³) (Cromer & Kronoveter, 1976; NIOSH, 1976; Röhm, 1994). It is difficult, however, to draw meaningful conclusions concerning levels of exposure that induced effects in these studies, as there was little attempt to assess mean versus peak exposures. Moreover, interpretation of several of the investigations is complicated by concomitant exposure of the examined populations to other substances.

In cases where this added value of epidemiological studies is limited, they are described very briefly in the text.

In cases, where there are numerous relevant and valid studies, details of individual study design and results could be presented in tabular format (for example, see Table 5 at the end of this annex), and summarized briefly in the text.

For epidemiological studies considered critical, descriptions should include the size of the population studied, study design, case identification, exposure and methods for its assessment, methods of analysis, possible sources of confounding and bias, and their treatment, results and their interpretation, and comments on the reliability of the study

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

1. Bioassays were conducted by Blum & Speece (1991) on three groups of bacteria: methanogens (anaerobes from an enrichment culture maintained for >10 years), aerobic heterotrophic bacteria, and *Nitrosomonas* obtained from the mixed liquor of an activated sludge wastewater treatment plant. Inhibition of gas production by methanogens, inhibition of oxygen uptake by aerobic heterotrophic bacteria, and inhibition of ammonia oxidation by *Nitrosomonas* were the end-points used in this study to evaluate toxicity. Varying degrees of sensitivities were exhibited; however, *Nitrosomonas*, with an IC₅₀ value of 1.4 mg/litre, was more sensitive than methanogens (IC₅₀ value of 4.1 mg/litre) and significantly more sensitive than aerobic heterotrophs (IC₅₀ value of 130 mg/litre).

The type and extent of the presentation on toxicity to aquatic and terrestrial organisms (other than those mentioned earlier sections) is dependent upon the size of the available dataset, and contribution to the overall assessment of environmental risks.

Based on bioluminescence, the 5-minute LC₅₀ for 1,1,2,2-tetrachloroethane was 5.4 mg/litre in a Microtox test using *Photobacterium phosphoreum* (Blum & Speece, 1991).

Unfed and fed *Daphnia magna* (first instar, <24 hours old) had similar measured 48-hour LC₅₀ values of 62 and 57 mg/litre, respectively, under static test conditions (Richter et al., 1983). With complete immobilization as the end-point, the 48-hour EC₅₀ values were 23 and 25 mg/litre for unfed and fed *D. magna*, respectively. LeBlanc (1980) conducted a similar test with *D. magna* at 22 C and reported nominal 24-hour and 48-hour LC₅₀

In cases (such as 1,1,2,2-tetrachloroethane) where available data are limited, the various end-points and associated effect levels may be summarized within the text.

values of 18 and 9.3 mg/litre, respectively. Pawlisz & Peters (1995) reported that prior exposure of *D. magna* to sublethal concentrations of 1,1,2,2-tetrachloroethane (6.3–50% of the 48-hour LC₅₀ of 0.095 mmol/litre) for 24 hours did not influence the body burden required to narcotize the animals upon subsequent exposure to the chemical at the LC₅₀.

The measured 28-day LOEC and no-observed-effect concentration (NOEC) for reproductive impairment in *D. magna* were 14.4 and 6.9 mg/litre, respectively, under flow-through conditions (Richter et al., 1983).

Numerous acute toxicity studies have been conducted on a variety of freshwater fish species; in general, 96-hour LC₅₀ values were very similar. Under flow-through conditions, the measured 96-hour LC₅₀s for 30-day-old fathead minnows (*Pimephales promelas*) were 20.3 and 20.4 mg/litre (Veith et al., 1983; Walbridge et al., 1983). In juvenile (2- to 4-month-old) flagfish, the measured 96-hour LC₅₀ for 1,1,2,2-tetrachloroethane in the flow-through toxicity test was 18.5 mg/litre; the nominal LC₅₀ value in a static-renewal 96-hour toxicity test was 26.8 mg/litre (ATRG, 1988; Smith et al., 1991). No adequate acute toxicity studies of marine fish were identified.

Chronic toxicity studies under flow-through test conditions were conducted on the early life stages of flagfish by ATRG (1988) and Smith et al. (1991). Egg hatchability was unaffected at a measured 1,1,2,2-tetrachloroethane concentration of 22.0 mg/litre, the highest concentration tested in both studies. The measured LOECs for reduced 10-day larval survival were 10.6 and 7.2 mg/litre, whereas the LOECs for 28-day juvenile survival were 11.7 and 8.5 mg/litre (ATRG, 1988; Smith et al., 1991). There were no statistically significant effects on the growth of 1-week-old fry over a 28-day exposure period, even at the highest concentration of 1,1,2,2-tetrachloroethane tested (11.7 mg/litre).

10.2 Terrestrial environment

No studies were identified on the effects of 1,1,2,2-tetrachloroethane on terrestrial organisms.

ADDITIONAL EXAMPLE

The effects of exposure to 1,2-dichloroethane on a number of aquatic organisms in the laboratory and field have also been investigated. In bacteria, the lowest reported IC₅₀s for inhibition of gas production and ammonia consumption were 25 and 29 mg/litre in methanogens and Nitrosomonas, respectively (Blum & Speece, 1991). The most sensitive freshwater alga studied was *Microcystis aeruginosa*, in which an EC₅₀ for inhibition of cell multiplication of 105 mg/litre was observed (Bringmann & Kühn, 1978); in the only identified study in marine algae, an EC₅₀ for carbon uptake of 340 mg/litre was reported in *Phaeodactylum tricorutum* (Pearson & McConnell, 1975). Toxicity thresholds (cell multiplication inhibition) were above 800 mg/litre for three species of aquatic protozoa (Bringmann & Kühn, 1980).

The lowest reported LC₅₀ value for *Daphnia* was 220 mg/litre (Leblanc, 1980), whereas the lowest EC₅₀ (for 10% immobilization) was 150 mg/litre (Freitag et al., 1994). Effects on reproductive success and growth were observed in *Daphnia* at 20.7 and 71.7 mg/litre, respectively. There were no effects on these end-points at 10.6 and 41.6 mg/litre, respectively (Richter et al., 1983).

Where appropriate for chemicals having larger datasets, ranges of effect levels for various end-points and species may be summarized within the text.

In cases where extensive data are available for many species, the information (including species, end-point(s), range of effect levels and literature citation) may be presented in tabular format, and briefly summarized within the text. Where appropriate, the lack of identified data should be mentioned in the text.

If specific physicochemical properties (e.g., water solubility, vapour pressure) are expected to significantly influence the bioavailability and/or toxicity for aquatic species, this should be discussed, particularly if only results based on nominal test substance concentrations are available.

In some cases (such as 1,2-dichloroethane) only the lowest-observed-effect levels for various end-points and species (i.e., the most sensitive species) can be summarized within the text.

Based on available data, the most sensitive freshwater vertebrate species appears to be the northwestern salamander, in which 9-day larval survival (4 days post-hatch) was reduced at 2.5 mg/litre (Black et al., 1982).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose-response assessment

1. Owing to the significant decline in the use of this substance, the toxicological profile of 1,1,2,2-tetrachloroethane has not been well characterized, with the available data being confined primarily to early limited studies.
2. Based on the results of studies in experimental animals, the acute toxicity of 1,1,2,2-tetrachloroethane is slight to moderate. The chemical may induce skin, eye, and mucosal irritation. Owing to the limitations of the available data in humans on effects associated with longer-term exposure to 1,1,2,2-tetrachloroethane, it is necessary to rely on information obtained from the limited studies in animals for determination of the critical effects and associated effect levels.
3. The results of available studies on the non-neoplastic effects of 1,1,2,2-tetrachloroethane in experimental animals exposed by ingestion or inhalation indicate that the liver is the principal target organ. However, the majority of subchronic and chronic studies are too limited to allow a confident determination of a NO(A)EL or LO(A)EL for hepatic or other effects, because of either the lack of information presented in the published accounts or the limitations of the study designs (e.g. small numbers of animals per experimental group, lack of histopathological examination, etc.).
4. Long-term exposure to 1,1,2,2-tetrachloroethane resulted in a significantly increased incidence of hepatocellular carcinomas in both male and female mice. However, no significant increases in tumours were observed in similarly exposed rats, although there was a non-statistically significant increase at the highest dose tested (which was lower, on a time-weighted-average basis, than the lowest dose to which mice were exposed), and both species were exposed only for up to 78 weeks. 1,1,2,2-Tetrachloroethane was a potent promoter, but did not act as an initiator, in an initiation/promotion assay. The weight of evidence of available *in vitro* and *in vivo* assays suggests that this substance is not genotoxic or that it is, at most, weakly genotoxic. Although available data are incomplete, it has been proposed that the liver tumours may be induced by mechanisms that may not be relevant to humans, for which humans are less susceptible, or for which there may be a threshold of exposure. In addition, it has been hypothesized that the carcinogenicity of 1,1,2,2-tetrachloroethane may be associated with the formation of free radicals, lipid peroxidation, or hepatic damage (such as focal necrosis associated with intense cellular proliferation) (Hanley et al., 1988; Larson & Bull, 1992; Paolini et al., 1992). Therefore, on the basis of data currently available, it is not possible to draw any firm conclusions with respect to the potential carcinogenicity of 1,1,2,2-tetrachloroethane in humans.

The first subsection 11.1.1 Hazard identification and dose-response assessment, includes weight of evidence considerations for all identified hazards as a basis for delineation of those considered critical for dose-response analyses.

In cases where a dose-response parameter is based upon carcinogenic effects, the basis for the selection and derivation of this parameter should be clearly specified in the text. Similarly for any critical end-point, the selection of the dose-response parameter (e.g., NO(A)EL, LO(A)EL, benchmark dose) should be clearly described within the text.

5. Owing to the limitations of available studies on the potential toxicological effects associated with exposure to 1,1,2,2-tetrachloroethane, it is not possible to confidently determine a NO(A)EL or LO(A)EL for non-neoplastic effects. The toxicological end-point for which the dose–response relationship is best characterized is the increase in hepatocellular carcinomas observed in the long-term bioassay in mice (NCI, 1978). It is noted, however, that the observed increases in tumour incidence are restricted to one species and that the weight of available data indicates that 1,1,2,2-tetrachloroethane is, at most, weakly genotoxic.

The weight of evidence with respect to potential carcinogenicity in humans should be clearly outlined in the text.

6. Based on multistage modelling of the incidence of hepatocellular carcinomas in male or female mice exposed to time-weighted-average doses of 0, 142, or 284 mg/kg body weight per day for up to 78 weeks, adjusted for continuous exposure for a standard duration of 104 weeks and corrected for the expected rate of increase in tumour formation in rodents in a standard bioassay of 104 weeks, the doses associated with a 5% increase in tumour incidence ($TD_{0.05}$) range from 5.8 to 28 mg/kg body weight per day.

In cases (such as 1,1,2,2-tetrachloroethane) where a dose-response parameter is based upon carcinogenic effects, the basis for the selection and derivation of this parameter should be clearly specified in the text.

ADDITIONAL EXAMPLE

7. Data on effects of methyl methacrylate in humans are informative primarily with respect to irritation and sensitization (for exposure both dermally and by inhalation) and carcinogenicity. Although there are some quantitative data on exposure to methyl methacrylate in available cross-sectional investigations of other end-points (NIOSH, 1976; Jedrychowski, 1982; Marez et al., 1993), they are considered inadequate as the principal basis for hazard identification and dose–response assessment owing to limitations of design and the potential role of confounding factors. Data on hazard identification and dose–response assessment for effects other than irritation/sensitization and carcinogenicity are derived primarily, therefore, from investigations in experimental animals.

8. The acute toxicity of methyl methacrylate is low. Irritation of the skin, eye, and nasal cavity has been observed in rodents and rabbits exposed to relatively high concentrations of methyl methacrylate. This substance is a mild skin sensitizer in animals. Methyl methacrylate is a mild skin irritant in humans and has the potential to induce skin sensitization in susceptible individuals. Although occupational asthma associated with methyl methacrylate has also been reported, there is no conclusive evidence that methyl methacrylate is a respiratory sensitizer.

9. The effect observed most frequently at lowest concentration after repeated inhalation exposure of experimental animals to methyl methacrylate is irritation of the nasal cavity. Effects on the kidney and liver at higher concentrations have also been reported.

Limited available data indicate that methyl methacrylate is unlikely to induce fetotoxic effects in the absence of maternal toxicity. There has been no evidence of reproductive toxicity, based on limited available data (a dominant lethal assay in mice and examination of the gonads in repeated-dose toxicity studies). Based on limited available data, neurological effects have been observed following ingestion of doses greater than those that induce minimal renal effects.

10. As a whole, the available epidemiological studies do not provide strong or consistent evidence of a carcinogenic effect of methyl methacrylate on any target organ in humans, nor can it be inferred with any degree of confidence that the possibility of an excess risk has been

disproved. Methyl methacrylate has not been carcinogenic in an extensive, well documented 2-year bioassay in rats and mice exposed by inhalation and in additional chronic inhalation studies in rats and hamsters. Although not mutagenic in vitro in bacterial systems, methyl methacrylate has been mutagenic and clastogenic in mammalian cells in vitro. In in vivo studies (primarily by the inhalation route) in which there has been clear evidence of toxicity within the target tissue, there has been limited evidence of genotoxicity of methyl methacrylate. On the basis of these observations, methyl methacrylate is considered unclassifiable with respect to carcinogenicity in humans.

11. Owing to the limitations of the available studies in humans on effects associated with longer-term exposure to methyl methacrylate, it is necessary to rely primarily on information obtained from the studies in animals for determination of critical effect levels. The lowest reported effect level for inhalation was 100 ppm (410 mg/m³) in rats exposed to methyl methacrylate for 2 years (based upon inflammatory degeneration of the nasal epithelium); the NOEL in this investigation was 25 ppm (102.5 mg/m³) (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997).

The basis for identification of the critical end-point(s) and selection of the appropriate dose-response parameter [e.g., NO(A)EL, LO(A)EL, benchmark dos] should be clearly described within the text (see example on methyl methacrylate)

11.1.2 Criteria for setting tolerable intakes and guidance values

12. As noted in section 11.1.1, the toxicological end-point for which the dose–response relationship is best characterized, and which might provide the basis for derivation of limits of exposure or for judgement of the quality of environmental media by relevant authorities, is the increase in hepatocellular carcinomas observed in the long-term bioassay in mice (NCI, 1978).

In Section 11.1.2 Criteria for setting tolerable intakes and guidance values, the basis and rationale for the derivation of tolerable intakes and/or guidance values based upon the considered critical end-point(s) are described. Derivation of a tolerable intake or guidance value is dependent upon the critical end-point(s) selected, available dose-response parameters, as well as the predominant route of human exposure.

13. A value, for example, 5000 or 50 000 times less than the TD_{0.05S} derived above might be considered conservative as a guidance value. This margin (5000–50 000) affords protection similar to that associated with the range for low-dose risk estimates generally considered by various agencies to be “essentially negligible” (i.e. 10⁻⁵ to 10⁻⁶). As, on the basis of available data, 1,1,2,2-tetrachloroethane is, at most, weakly genotoxic, a smaller margin (e.g. 1000) might also be considered appropriate. As available data indicate that air is the principal medium of human exposure, the most conservative of these approaches result in, for example, a range of airborne concentrations of 3.4–16 µg/m³ or 0.34–1.6 µg/m³, respectively. Corresponding values for ingestion are 1.2–5.6 µg/kg body weight per day or 0.12–0.56 µg/kg body weight per day. It should be noted, however, that these possible guidance values for air have been extrapolated directly from a study in which the chemical was administered orally to experimental animals. Although there may be substantial variations in toxicokinetics following exposure to 1,1,2,2-tetrachloroethane by different routes, available data are inadequate to quantitatively account for these differences in the derivation of guidance values.

Where appropriate (as shown for the example of 1,1,2,2-tetrachloroethane) limitations of the proposed tolerable intake guidance value should be mentioned in the text.

ADDITIONAL EXAMPLE

14. The following quantitative guidance is provided as an example of a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities. As methyl methacrylate is considered to be “unclassifiable with respect to carcinogenicity in humans,” guidance values are derived on the basis of a lowest-observed-(adverse)-effect level [LO(A)EL] or a no-observed-(adverse)-

The rationale and data forming the basis of the decision to derive a tolerable intake/guidance value concentration, is clearly outlined within the text.

effect level [NO(A)EL] for non-neoplastic effects. For methyl methacrylate, the route of exposure most relevant to the general population is likely inhalation.

15. The value considered most appropriate as a basis for development of a tolerable concentration in air is the NOEL of 25 ppm (102.5 mg/m³) in rats exposed to methyl methacrylate for 2 years (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997). Effects at the next higher concentration were degenerative changes in the olfactory epithelium.

16. The pattern of the critical effects of inhalation of methyl methacrylate in animal studies (i.e. the olfactory epithelium being affected at lowest concentration) is consistent with toxicity resulting from metabolism of the inhaled material in the olfactory tissue by carboxylic esterases to methacrylic acid. Data on species differences in olfactory tissue carboxylesterase activity have not been identified; however, based on limited data from human tissue samples that may not have been morphologically normal taken at polyp biopsy, the activity of alpha-naphthylbutyrate carboxylesterase in human nasal respiratory tissue is less than that in the rat (Mattes & Mattes, 1992).

17. Although it is possible that humans may be less sensitive than rodents to lesions of the nasal epithelium caused by methyl methacrylate, currently available data are inadequate to account quantitatively for potential interspecies variation in sensitivity. However, studies that are currently under way may shed some additional light on this aspect (T. Green, personal communication, 1997; P.J. Pinto, personal communication, 1997). Therefore, on the basis of the available data, a tolerable concentration (TC) has been derived on the basis of a commonly adopted default value of 10-fold for interspecies variation as follows:

$$\begin{aligned} \text{TC} &= (102.5 \text{ mg/m}^3/100) \times (6/24) \times (5/7) \\ &= 0.2 \text{ mg/m}^3 \text{ (rounded to one significant figure)} \end{aligned}$$

where:

- 102.5 mg/m³ (25 ppm) is the lowest NOEL reported in inhalation bioassays of adequate quality in animal species (rats) conducted to date (exposure-related and concentration-dependent microscopic changes [degeneration/atrophy of the olfactory epithelium and underlying Bowman's glands, hyperplasia of basal (reserve) cells, replacement of olfactory epithelium by ciliated (respiratory-like) epithelium, and inflammation of the mucosa and/or submucosa] were observed in anterior portions of the nasal cavity in rats exposed to the next higher concentration) (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997);
- 6/24 and 5/7 are the conversion of intermittent exposure of rats (i.e. 6 hours/day, 5 days/week) to continuous exposure of humans; this is appropriate in view of data that suggest that continuous exposure to methyl methacrylate could result in effects at concentrations below the NOAEL for intermittent exposure (Lomax et al., 1994); no scaling factor for inhalation volume to body weight was used, as effects at the next higher dose level are limited to the site of entry; and

100 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation).

In cases (such as methyl methacrylate) in which the tolerable intake is derived on the basis of a NO(A)EL, LO(A)EL, or benchmark dose, the selection and application of uncertainty factors in the calculation of tolerable daily intakes or tolerable concentrations, must be clearly outlined within the text. Use of the format illustrated in this example for methyl methacrylate is encouraged.

18. Based on the results of limited available cross-sectional studies on respiratory effects in human populations, this value is likely to be protective.

19. A TDI can be derived for the oral route of exposure based on a 2-year drinking-water study in rats in which the NOAEL in females was considered to be 146 mg/kg body weight per day; the NOEL in males was 121 mg/kg body weight per day, the highest dose level tested (Borzelleca et al., 1964). Incorporating an uncertainty factor of 100 ($\times 10$ for intraspecies variation; $\times 10$ for interspecies variation), the TDI would be 1.2 mg/kg body weight per day.

ADDITIONAL EXAMPLE

20. On the basis that the carcinogenicity of o-toluidine may involve a genotoxic mechanism, it is not possible to reliably identify a threshold at which exposure to o-toluidine would not result in some risk to human health.

11.1.3 Sample risk characterization

21. Although data are insufficient to allow the confident determination of a LO(A)EL or NO(A)EL for 1,1,2,2-tetrachloroethane, minimal effects in rodents have been observed only at levels more than 50 000 times greater than those in the principal medium of exposure (air) in the general environment.

22. Based on a sample estimate of exposure, indirect exposure in the general environment is 14 to >160 or 1.4 to >16 times less than guidance values that might be derived on the basis of available data on the dose–response relationship for liver tumour induction in mice (i.e. the $TD_{0.05S}$ divided by 5000 or 50 000, or 3.4–16 $\mu\text{g}/\text{m}^3$ or 0.34–1.6 $\mu\text{g}/\text{m}^3$, respectively). It should also be noted, however, that indirect exposure in the general environment is likely overestimated here, as it is based on the range of mean concentrations for detected values, although 1,1,2,2-tetrachloroethane was detected in only approximately 50% of samples.

ADDITIONAL EXAMPLE

23. The extremely limited nature of the available data as a basis for estimation of exposure should be borne in mind in interpreting the comparisons presented here for predicted indirect population exposure in the general environment and estimated exposure from the use of consumer products containing methyl methacrylate. Moreover, the sample exposure estimates presented in section 6.2 will vary considerably as a function of production and use patterns and control measures in various countries.

24. Based upon the sample predicted concentration (based on fugacity modelling) of methyl methacrylate in air of $2.44 \times 10^{-4} \mu\text{g}/\text{m}^3$, presented in section 6.1, levels of methyl methacrylate in ambient air are many orders of magnitude less than the calculated tolerable concentration of 200 $\mu\text{g}/\text{m}^3$. Estimated intakes associated with inhalation exposure (predicted by computer modelling) during the use of consumer products containing methyl methacrylate, such as dispersion paints (estimated to be in the 10–100 $\mu\text{g}/\text{kg}$ body weight per day range) and oil-based paints (predicted exposure in the 100–1000 $\mu\text{g}/\text{kg}$ body weight per day range) (see section 6.2), may be up to an order of magnitude higher than the tolerable intake associated

Authors should indicate those cases, in which the derivation of atolerable intake or guidance value may not be considered appropriate or feasible.

Section 11.1.3 Sample risk characterization is intended to provide examples of how risks of certain populations might be characterized, based upon the toxicological and exposure information presented within the CICAD.

Thus the sample risk characterization(s) presented in a CICAD do not necessarily represent all possible exposure situations, but are provided as example and guidance only. Authors are encouraged to indicate within the text of this section that it is recognized that there are a number of different approaches to assessing the risks to human health posed by chemicals, and since exposure estimates vary as a function of use patterns, the risk characterization presented here is provided only as an example, primarily for illustrative purposes. In contrast to other sections of the CICAD, it is thus not necessarily applicable for populations elsewhere but is rather, as the heading implies, an

with exposure at the level of the tolerable concentration. Although it has been reported that in some countries these products are not supplied to the general public, information on use patterns of these products in other countries was not available.

example only.

25. With respect to occupational exposure, mean levels of methyl methacrylate in the air of production and manufacturing facilities and dental facilities range up to several hundred mg/m³, whereas levels in beauty salons are generally less than 100 mg/m³ (IARC, 1994). Elevated levels (greater than 1500 mg/m³) during floor coating with methyl methacrylate-containing resins have been reported, although time-weighted-average concentrations would be less.

Depending upon the available data, the sample risk characterization may encompass potential risks to the general public and/or occupationally exposed individuals.

ADDITIONAL EXAMPLE

27. Due to the nature of use, patterns of release and environmental fate of DMF, the focus of the human health risk characterization for indirect exposure is populations exposed through air in the vicinity of industrial point sources.

28. With a reported annual loading of less than 20 tonnes and generally less than 1 tonne at any location in the sample country, continuous releases of consistent magnitude likely result in long term exposure to small concentrations (worst-case estimate in sample country, 0.11 mg/m³), of DMF near point sources. Because of the absence of empirical data on concentrations of DMF in air in the sample country, an EEV was calculated based on release data for the largest Canadian emitter, making several conservative assumptions.

29. The largest annual release reported at one location can be expressed on a daily basis (12.7 tonnes/year = 0.0348 tonnes/day or 3.48 x 10⁷ mg/day). As a conservative estimate, it will be assumed that daily releases of DMF are contained within a cylinder having a radius of 1 km centered on the point-source. Dispersion within 1 km is likely a conservative assumption for a number of reasons. First, the greatest reported emissions are occurring in a mixed industrial and agricultural area (Environment Canada 1999b). The site is paved with asphalt, and as such wild plants and mammals will not likely be found in the immediate vicinity of the source. Finally, although the specific dispersal behavior of DMF has not been documented near the source, results of dispersion modeling indicate that concentrations of other contaminants released to air elsewhere tend to decrease rapidly within a few kilometers of industrial point-sources (e.g. Davis 1997, Lakes Environmental Consultants 1998).

30. Upward movement of organic compounds generally does not exceed 100 m at night and may exceed 1000 m during the day (Bunce 1998a). The more conservative value of 100 m will be used as a ceiling for estimating the exposure concentrations throughout the day.

31. This provides a dispersal volume of 3.14 X 10⁸ m³ in the form of a cylinder of 100 m in height and 1 km in radius. With a daily release of 3.48 x 10⁷ mg/day, the daily increase in the concentration of DMF in air is estimated at 0.11 mg/m³. Since ambient levels in the cylinder are likely to be lower than this daily increase of 0.11 mg/m³, it will be used as a conservative estimated exposure value (EEV). Reaction with hydroxyl radical will tend to reduce the concentrations of DMF in the daytime. Since the degradation half-life of DMF could be a week or more,

continuous daily inputs would lead to build-up of DMF within the cylinder in the absence of any other loss process. However, fugacity-based modelling suggests that advection processes, i.e. rain and wind, are the major factors in determining concentrations in the atmosphere. Even under essentially stagnant conditions, with a wind speed of 1 km/hour, the rate of advection of DMF out of the cylinder is so fast that the steady-state concentration would be 0.01 mg/m³ or less. At a typical average wind speed of 10 km/hour, the concentration of DMF in the cylinder would be reduced by a factor of approximately 100. The estimated exposure value (EEV) of 0.11 mg/m³ is generally higher or comparable to measurements made in other countries.

32. Worst-case estimates of airborne levels in the immediate vicinity of the largest emitter in the sample country (0.11 mg/m³), which are likely 10-100-fold greater than those anticipated under most conditions, do not appreciably exceed the TC (0.1 mg/m³) derived on the basis of increases in serum hepatic enzymes in exposed workers.

ADDITIONAL EXAMPLE

11.3.1.1 Exposure of the sample population

1. The principle source of environmental exposure to butadiene is air. Although few data were identified regarding levels in drinking water and food, due to its physical/chemical properties (e.g., vapour pressure and partition coefficients) and environmental release patterns (i.e., principally atmospheric emissions), intake of butadiene in these media is expected to be negligible in comparison to that in air.
2. As an example of population exposure characterization, estimates are presented on the basis of data available for Canada. Based on concentrations measured in outdoor in several rural, suburban and urban locations across Canada (Dann, 1997) (see Section 6.1.1), 95% of the general population can be expected to be exposed to average concentrations of up to 1.0 µg/m³. However, since levels are generally greater in highly urbanized areas, estimated "reasonable worst-case exposure" is expected to be up to 1.3 µg/m³ (95th percentile). In areas influenced by industrial point sources, exposure could be as high as 6.4 µg/m³, based on the 95th percentile of concentrations measure near a source in Ontario, Canada (MOEE, 1995).
5. Individuals may also be exposed to butadiene for short durations while at self-service gasoline filling stations or in parking garages; however, these intakes are still much less than average daily intakes for the general population from inhalation of background concentrations in outdoor and indoor air.
6. Although available Canadian data indicate that butadiene is detected with greater frequency in indoor air than in outdoor air, there are insufficient data to characterize the distributions of concentrations of butadiene in various indoor environments. In general, butadiene is detected more frequently and at higher concentrations in indoor environments contaminated by environmental tobacco smoke, than in areas where smoking does not occur. Non-smokers who spend a considerable proportion of their time spent in indoor environments where ETS is present can be exposed to concentrations of butadiene which are an order of magnitude higher than the average levels in the outdoor air. Tobacco use

Where the available information allows, this section may be divided in two parts:

*11.1.3.1 Exposure of the sample population and
11.1.3.2 Health risks in the sample population*

National limits can be given in the sample risk characterization, provided that there is a full explanation of the process.

(e.g., 20 cigarettes per day) can increase the daily intake of butadiene by smokers by five times over the daily intake by non-smokers in ETS-contaminated indoor locations. The daily intake of butadiene by smokers can be 100 times greater than the daily intake of non-smokers who are not exposed to ETS.

11.1.3.2 *Health risks in the sample population*

1. Butadiene is released to air from both industrial point sources and more dispersive, non-point sources, the latter due to its production primarily during incomplete combustion. Based on estimates derived using monitoring data from Canada, intake for the general population is primarily from air, with intake from other media likely being negligible in comparison. The focus of the human health risk characterization is, therefore, the general population exposed in outdoor and indoor air in the general environment and those exposed through air in the vicinity of industrial point sources.
2. For compounds such as butadiene, where data are sufficient to support a plausible mode of action for induction of tumours by direct interaction with genetic material, estimates of exposure are compared with quantitative estimates of cancer potency to characterize risk.
3. Tumorigenic concentrations were calculated on the basis of data from both epidemiological studies and investigations in experimental animals. For the critical epidemiological investigation (Delzell et al., 1995), a TC_{01} (i.e., the concentration associated with a 1% increase in mortality due to leukemia) was considered the appropriate measure of carcinogenic potency, since the majority of the observable data fell within this range. Although four different mathematical models were considered, the TC_{01} generated by the model with the best fit was 1.7 mg/m^3 .
4. Quantitative estimates of carcinogenic potency derived on the basis of data in experimental animals were calculated as TC_{05s} (i.e., the concentration associated with a 5% increase in tumour incidence). Based on the 2-year bioassay in mice (NTP, 1993), TC_{05s} ranged from 2.3 mg/m^3 (95% LCL = 1.7 mg/m^3) to 99 mg/m^3 (95% LCL = 23 mg/m^3). The TC_{05s} derived on the basis of the more limited study in rats (Hazleton Laboratories Europe Ltd., 1981a) ranged from 6.7 mg/m^3 (95% LCL = 4.7 mg/m^3) to 4872 mg/m^3 (95% LCL = 766 mg/m^3).
5. The values derived on the basis of studies in humans are preferred as the basis for comparison with estimates of exposure to characterize risk. While there are a number of uncertainties in the use of the epidemiological data for both hazard evaluation and exposure–response analyses (Section 10.3.3), these are likely far less than uncertainties associated with interspecies extrapolation. Moreover, estimated potency for humans is similar to that developed on the basis of the cancer bioassays in experimental animals. (Indeed, although in an area of the exposure–response curve where data were more sparse, it is noteworthy that TC_{05s} calculated on the basis of epidemiological data [as opposed to the TC_{01s} presented above] are within the range of values derived from the studies in rodents.)
6. Based on the sample exposure scenarios presented above (Section 10.3.1), 95% of the population in Canada is exposed to concentrations of butadiene in outdoor air of $1.0 \text{ } \mu\text{g/m}^3$ or less. For the proportion of the

general population that is regularly exposed to higher concentrations of butadiene in urban areas (i.e., the “reasonable worst-case scenario”), the 95th percentile of the distribution of concentrations is $1.3 \mu\text{g}/\text{m}^3$. In the only area of Canada identified as having an industrial point source, the 95th percentile of the distribution of concentrations is $6.4 \mu\text{g}/\text{m}^3$.

7. The margins between carcinogenic potency and estimated exposure for the general population (including ambient and reasonable worst case) and those in the vicinity of a point source are presented in the table below. Equivalent low dose risk estimates are also presented in this table. (Table 1)

8. In view of the relative potency of butadiene to induce some non-cancer effects, these endpoints are also important in risk characterization. As presented above, a benchmark concentration (BMC_{05}) of $0.57 \text{ mg}/\text{m}^3$ (95% LCL = $0.44 \text{ mg}/\text{m}^3$) was derived on the basis of data for the incidence of ovarian atrophy of all severities (i.e., female reproductive toxicity) in mice exposed to butadiene for up to 2 years (NTP, 1993). And while there is uncertainty about the relevance of the ovarian atrophy observed in mice for humans (Section 10.3.3), the BMC_{05} is slightly less than the lower end of the range of estimates of cancer potency based on the incidence of tumours in the same study in mice, as well as the TC_{05} for cancer based on the epidemiological data. The mode of induction of ovarian atrophy is unknown. However, if it is (reasonably) assumed that the mode of action is related to that by which tumours are induced (i.e., direct interaction with genetic material), risk to human health for reproductive effects may be characterized in the same manner as presented for cancer. Therefore, estimates of the margin between the BMC_{05} for ovarian toxicity and a sample exposure characterization, and the equivalent low dose risk estimates, are presented in the table below. It should be noted, though, that even if the mode of induction of ovarian atrophy does not involve direct interaction with genetic material, the margin between exposure and effect level (i.e., for which a tolerable concentration is normally developed) is still small — i.e., exposure levels in Canada are 90–570 times lower than the benchmark concentration, as presented below Table 2).

11.1.4 *Uncertainties in the evaluation of health risks*

ADDITIONAL EXAMPLE: DIMETHYLFORMAMIDE

33. Quantitative estimates of ambient levels of DMF in the vicinity of point sources in the sample country on which the human health risk characterization is based are highly uncertain (see discussion of uncertainty in section 11.2) and likely conservative, although consistent with highest concentrations measured in other countries. The proximity of these predicted concentrations in the vicinity of point sources to residential areas is also unknown. Available monitoring data are inadequate as a basis for characterization of the exposure of the general population to DMF.

34. There is a high degree of confidence based on studies in both humans and experimental animals that the liver is the target organ for the toxicity of DMF. Cross-sectional studies on hepatic effects in workers, limited principally to males, were complicated by co-exposures to other substances and limitations of available data on exposure, including, in some cases, lack of monitoring data for individuals. However, the levels that induced minimally adverse effects were remarkably consistent across a large number of studies. The tolerable concentration developed on the basis

This section describes the uncertainties in all stages of the health risk evaluation, i.e., hazard identification, exposure-response assessment, criteria for setting tolerable intakes/guidance values, and sample risk characterization

of increases in serum hepatic enzymes in occupationally exposed populations is likely conservative since it does not take into account additional exposure by the dermal route.

ADDITIONAL EXAMPLE, FORMALDEHYDE

52. With respect to toxicity, the degree of confidence that critical effects are well characterized is high. A relatively extensive database in both humans and animals indicates that critical effects occur at the initial site of exposure to this substance. The database in humans is also sufficiently robust to serve as a basis for confident conclusion concerning the consistently lowest levels at which effects (i.e., sensory irritation) occur, although additional investigation of an unconfirmed report of effects on respiratory function in children exposed to lower levels of formaldehyde is desirable.

53. The degree of confidence in the database that supports an obligatory role of regenerative proliferation in the induction of nasal tumours in rats is moderate to high, although the mechanism of carcinogenicity of formaldehyde is unclear. Although the biologically motivated case-specific model for estimation of cancer risks is clearly preferred due to incorporation of as many biological data as possible, there are a number of uncertainties described in more detail in CIIT (1999) and summarized briefly here, although sensitivity analyses were not conducted. For dosimetry, sources of uncertainty for which sensitivity analyses would have been appropriate include the use of individual rat, primate and human nasal anatomies as representative of the general population, the use of a typical-path human lung structure to represent people with compromised lungs, the sizes of specific airways, the use of a symmetric Weibel model for the lung, the estimation of the location and extent of squamous and olfactory epithelium and of mucus- and non-mucus-coated nasal regions in the human, and the values of mass transfer and dispersion coefficients. The lack of human data on formaldehyde-related changes in the values of key parameters of the clonal growth model accounts for much of its uncertainty.

54. In order to better define the mode of action of induction of tumours, elaboration of the quantitative relationship between DPX and mutation and the time course of loss of DNA-protein crosslinks is desirable. Additional characterization of the shape of the concentration-response relationship for regenerative proliferative response would also be informative.

55. Comparison of the output of the biologically motivated case-specific model with that for the comparable value for default methodology (i.e., estimation of tumorigenic concentrations close to the experimental range), indicates that values for the former are at least three orders of magnitude less than that for the latter.

11.2 Evaluation of environmental effects

1. 1,1,2,2-Tetrachloroethane is released to the environment principally in emissions to ambient air, where it is moderately persistent. Because of its volatility, rapid photo-oxidation in the atmosphere, and an atmospheric ozone-depleting potential of less than 0.001 relative to CFC-11, 1,1,2,2-tetrachloroethane is not expected to contribute significantly either to the depletion of the stratospheric ozone layer or to global warming.

In Section 11.2, Evaluation of environmental effects, effects on organisms with the greatest potential for exposure (based upon the level and route of releases as well as fate within the environment) should be emphasized.

2. Terrestrial organisms have the greatest potential for exposure to 1,1,2,2-tetrachloroethane in ambient air in the environment. However, no data were identified on the effects of 1,1,2,2-tetrachloroethane in terrestrial species. Therefore, it is not possible to characterize the risk to these organisms associated with levels of 1,1,2,2-tetrachloroethane present in the environment.

3. Although 1,1,2,2-tetrachloroethane may be released to surface waters in industrial effluents, it is rapidly removed by volatilization. Based on the results of several studies in aquatic bacteria, invertebrates, and fish, effect levels are generally greater than 1 mg/litre. Although data are limited, concentrations of 1,1,2,2-tetrachloroethane in surface waters are generally much less than this value (at least two orders of magnitude). Therefore, it is likely that 1,1,2,2-tetrachloroethane does not pose significant risk to aquatic organisms.

Effects such as ozone depletion should also be addressed where possible. The data and assumptions used in the assessment of risks to environmental organisms should be clearly specified within the text.

In cases where relevant data are lacking, the text in this section should indicate that an assessment of possible effects on environmental organisms could not be conducted.

Especially when the database is extensive, it may be advisable to present the evaluation in graphic form. A number of examples, encompassing datasets of varying complexity are presented here.

ADDITIONAL EXAMPLE, LIMONENE

4. Limonene and other terpenes are released in large amounts mainly to the atmosphere. When released to soil or water, limonene is expected to evaporate to air to a significant extent, owing to its high volatility. Thus, the atmosphere is the predominant environmental sink of limonene, where it is expected to rapidly undergo gas-phase reactions with photochemically produced hydroxyl radicals, ozone, and nitrate radicals. The oxidation of terpenes, such as limonene, contributes to aerosol and photochemical smog formation. Ozonolysis of limonene may also lead to the formation of hydrogen peroxide and organic peroxides, which have various toxic effects on plant cells and may be part of the damage to forests observed in the last decades (Peters et al., 1994). Emissions of biogenic hydrocarbons such as limonene and other terpenes to the atmosphere may either decrease ozone concentrations when nitrogen oxide concentrations are low or, if emissions take place in polluted air (i.e. containing high nitrogen oxide levels), lead to an increase in ozone concentrations.

In cases where relevant data are lacking, the text in this section should indicate that an assessment of possible effects on environmental organisms could not be conducted.

5. Terrestrial organisms are most likely to be exposed to limonene via the air. The few studies on terrestrial species (i.e. insects) using vapour exposure reveal effects of limonene at parts per million levels. Measured environmental concentrations are typically around 0.1–2 ppb (0.6–11 $\mu\text{g}/\text{m}^3$), indicating a low risk for acute toxic effects on terrestrial organisms from direct exposure to limonene in air. At polluted sites, limonene concentrations in soil (up to 920 mg/kg soil) may exceed effect levels of soil-living organisms (e.g. earthworm, acute $\text{LC}_{50} = 6.0$ ppm; mg/kg).

6. In the aquatic environment, limonene exhibits high acute toxicity to fish and Daphnia. It may also bioaccumulate. The lowest acute toxicity value identified was 0.4 mg/litre (48-hour EC_{50} for Daphnia). Because

concentrations of limonene in surface waters of “polluted” and “unpolluted” areas are at least about 250 and 20 000 times lower than this acute toxicity value, respectively, it is likely that limonene poses a low risk for acute toxic effects on aquatic organisms. No studies were identified on chronic effects, and therefore risks associated with chronic exposures of aquatic organisms to limonene in “polluted” waters cannot be determined.

ADDITIONAL EXAMPLE, METHYL METHACRYLATE

7. Because of its release principally in emissions from industrial sources and its relatively high volatility, the atmosphere is the predominant environmental sink for methyl methacrylate. It is highly reactive with hydroxyl radicals; thus, its lifetime in the atmosphere is short. Substances whose atmospheric half-lives do not exceed 1 year are not considered to contribute to global warming; therefore, methyl methacrylate is not considered to be a greenhouse gas, nor would it contribute directly to depletion of the ozone layer. Methyl methacrylate is not expected to bioconcentrate in the environment. Terrestrial organisms will have the greatest potential for exposure to methyl methacrylate in ambient air. However, as no field or laboratory studies on birds, terrestrial invertebrates, or terrestrial plants were identified, the toxicity of methyl methacrylate to these organisms could not be assessed. Chronic studies on laboratory mammals are available, however, as well as data on levels of exposure of aquatic-based mammals to methyl methacrylate, thus permitting the comparison between effects and environmental exposure for these organisms. The mink was chosen as the model species, with aquatic organisms comprising up to 100% of its diet. Based on the concentrations of methyl methacrylate in air, water, and fish predicted by fugacity modelling and assuming daily consumption rates for mink of 0.55 m³ of air, 0.1 litre of water, and 158 g of fish, the estimated total daily intake of methyl methacrylate by mink in southern Ontario, Canada, is 0.17 ng/kg body weight per day, with approximately 80% of the exposure being attributable to inhalation (Government of Canada, 1993). The lowest NOEL observed in chronic inhalation studies in laboratory animals is 102.5 mg/m³, based on exposure-related and concentration-dependent microscopic changes in anterior portions of the nasal cavity (degeneration/atrophy of the olfactory epithelium and underlying Bowman’s glands, hyperplasia of basal cells, replacement of olfactory epithelium by respiratory epithelium, and inflammation of the mucosa and/or submucosa) (Rohm & Haas, 1979a; Lomax, 1992; Lomax et al., 1997). Using a factor of 10 to account for interspecies variability in sensitivity, the NOEL is 10⁸ times higher than levels predicted to occur in the environment in Canada (i.e. 0.24 ng/m³).

8. No chronic studies on aquatic organisms were identified; however, acute tests have been conducted on fish, *Daphnia magna*, and algae. The most sensitive effect was the onset of inhibition of cell multiplication by the green alga *Scenedesmus quadricauda* at 37 mg/litre following 8 days of exposure. This is similar to the concentration (i.e. 40 mg/litre) at which sublethal/ behavioural responses were noted in rainbow trout following 96 hours of exposure. Using a factor of 20 to convert from an acute to a chronic end-point and another factor of 10 to account for interspecies variability in sensitivity, the estimated effects threshold is approximately 10⁶-fold higher than the concentration predicted to occur in surface water in Canada (i.e. 0.13 ng/litre).

The data and assumptions used in the assessment of risks to environmental organisms should be clearly specified within the text (see example on methyl methacrylate).

9. Therefore, although available data on the environmental effects of methyl methacrylate are limited and predicted concentrations in various media are highly uncertain, a wide margin exists between observed effect levels and uncertain predicted environmental concentrations of methyl methacrylate. As such, the concentrations of methyl methacrylate predicted to be in the environment are unlikely to pose a risk to aquatic or terrestrial organisms.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

1. The International Agency for Research on Cancer (IARC, 1987) has classified 1,1,2,2-tetrachloroethane in group 3 (not classifiable as to its carcinogenicity to humans), based on inadequate evidence of carcinogenicity in humans and limited evidence in animals.

ADDITIONAL EXAMPLE

2. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated 1,2-dichloroethane on three occasions (WHO, 1971, 1980, 1992). In its last evaluation, the Committee concluded that this compound is genotoxic in both in vitro and in vivo test systems and carcinogenic in mice and rats when administered by the oral route. No acceptable daily intake (ADI) was therefore allocated. The Committee expressed the opinion that 1,2-dichloroethane should not be used in food.

3. In the current WHO Guidelines for drinking-water quality (WHO, 1993), the concentrations of 1,2-dichloroethane in drinking-water estimated to be associated with excess risks of 10^{-4} , 10^{-5} , and 10^{-6} are 300, 30, and 3 µg/litre, respectively, based on linear multistage modelling of the incidence of haemangiosarcomas in male rats in the NCI (1978) study.

REFERENCES

- Arthur CL, Pratt K, Motlagh S, Pawliszyn J (1992) Environmental analysis of organic compounds in water using solid phase micro extraction. *Journal of high resolution chromatography*, 15(11):741–744.
- ATRG (1988) *Aquatic toxicity of multiple organic compounds, Part II: Chlorinated ethanes and chlorinated ethylenes, summary report (interim)*. Prepared by the Aquatic Toxicity Research Group for the Ontario Ministry of the Environment, Lakehead University, Thunder Bay, Ontario, 95 pp.
- ATSDR (1994) *Toxicological profile for 1,1,2,2-tetrachloroethane* (draft). Atlanta, GA, US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.
- Gohlke R, Schmidt P (1972) [Subacute action of low concentrations of chlorinated ethanes with and without additional ethanol treatment in the rat.] *Internationales Archiv für Arbeitsmedizin*, 30:299–312 (in German).
- IARC (1987) *Overall evaluations of carcinogenicity: an updating of IARC monographs Volumes 1 to 42*. Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7).
- IPCS (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 170).

The information presented in this section should refer to previous comprehensive international evaluations conducted by IOMC organizations (Inter-Organization Programme for the Sound Management of Chemicals; includes WHO, FAO, UNEP, ILO, UNITAR, UNIDO and OECD).

The basis for the conclusions reached in the international evaluations mentioned in this section are very briefly summarized within the text of the CICAD.

References are listed in alphabetical order. Use of reference managing programmes is recommended, in order to ensure consistent reference formatting.

Some examples of presentations for various types of cited documents are provided here.

- Little AD (1983) *Cell transformation assays of 11 chlorinated hydrocarbon analogs (final report)*. US Environmental Protection Agency, Office of Toxic Substances (ICAIR Work Assignment No. 10; Document No. 40+8324457) [cited in ATSDR, 1994].
- NIOSH (1994) *NIOSH pocket guide to chemical hazards*. US Department of Health and Human Services, Public Health Service, Center for Disease Control and Prevention, National Institute for Occupational Safety and Health, June.
- NTP (1986) *Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344/N rats and B6C3F₁ mice (inhalation studies)*. Research Triangle Park, NC, US Department of Health and Human Services, National Institutes of Health, National Toxicology.

APPENDIX 1 — SOURCE DOCUMENTS**Government of Canada (1993)**

Copies of the *Canadian Environmental Protection Act (CEPA) Priority Substances List Assessment Report* for 1,1,2,2-tetrachloroethane (Government of Canada, 1993) may be obtained from the:

Environmental Health Centre

Health Canada

Address Locator: 0801A

Tunney's Pasture

Ottawa, Ontario

Canada K1A 0L2

Copies of the unpublished Supporting Documentation related to human health effects that formed the basis for preparation of the above-mentioned report may be obtained from the Environmental Health Centre at the address noted above.

Initial drafts of the Supporting Documentation and Assessment Report for 1,1,2,2-tetrachloroethane were prepared by staff of Health Canada and Environment Canada. The environmental sections were reviewed externally by Dr P. Cammer (Cammer and Associates), Dr D. Muir (Department of Fisheries and Oceans), Dr D. Singleton (National Research Council of Canada), and Dr K. Woodburn (Dow Chemical Canada Inc.). Sections related to the assessment of human exposure and health effects were peer reviewed by Dr J. Domoradzki (Dow Chemical Company, USA, Supporting Documentation only), Dr R. Bull (Washington State University, USA), and the Information Department of BIBRA Toxicology International, UK.

ADDITIONAL EXAMPLE**Agency for Toxic Substances and Disease Registry (ATSDR, 1994)**

Copies of the draft ATSDR profile for 1,1,2,2-tetrachloroethane (ATSDR, 1994) may be obtained from:

Agency for Toxic Substances and Disease Registry

Division of Toxicology/Toxicology Information Branch

1600 Clifton Road, NE, E-29

Atlanta, Georgia 30333

USA

The profile has undergone the following ATSDR internal reviews: Green Border Review, Health Effects Review, Minimal Risk Level Review, and Quality Assurance Review. In addition, a peer review panel, which included Dr M. Alexander (Cornell University, USA), Mr L. Skory (private consultant, USA), and Dr J. Withey (Health Canada), was assembled.

Appendix 1 lists the source document(s) upon which the CICAD is based, its availability as well as the nature of its scientific peer review.

Appendix 1 should be included in all drafts of CICADs.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 1,1,2,2-tetrachloroethane 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

International Agency for Research on Cancer, Lyon, France

Ministry of Health and Welfare, Government of Japan, Tokyo, Japan

National Institute for Working Life, Solna, Sweden

United States Environmental Protection Agency (Office of Pollution Prevention and Toxics, Washington, DC, USA; National Center for Environmental Assessment, Office of Research and Development, Research Triangle Park, USA).

Appendix 2 lists the individuals and institutions (and their locations; city & country) from which comments on the draft CICAD were received during the second-stage international peer review of the document.

The standard wording in the first paragraph of Appendix 2 is provided in the CICAD template provided by the Secretariat

Individuals and institutions are listed alphabetically.

Appendix 2 will be prepared by the Secretariat and is included in draft CICADs submitted for Final Review Board review and approval.

In Appendix 3, The members of the CICAD final review board, together with their affiliations, are listed, separately for members, observers, and secretariat..

APPENDIX 3 - CICAD FINAL REVIEW BOARD**INTERNATIONAL CHEMICAL SAFETY CARD**

[TO BE INSERTED BY IPCS]

The International Chemical Safety Card will be inserted by the IPCS Secretariat for reproduction within the CICAD.

TABLES

Examples of selected tabulated data included in CICADs are presented as guidance on types of presentations. When tables are used, all data should be in the tables and the text should only summarize what is in the tables.

Table 1: Levels of 1,1,2,2-tetrachloroethane in various media.

Medium	Location	Year	Concentrations	Reference
Ambient air	Canada	1989–1990	<0.1–0.25 µg/m ³ (means)	Environment Canada, unpublished data, 1992
Ambient air	USA	pre-1987	0.7 µg/m ³ (mean)	Shah & Heyerdahl, 1988
Surface water	Canada	1985	<1.0–4.0 µg/litre	COARGLWQ, 1986
Surface water	USA	1980–1988	<0.005–0.06 µg/litre	Kaiser & Comba, 1983
Surface water	Japan	1976	<0.001, <0.002, <0.05 µg/litre	Environment Agency Japan, 1976
Surface water	Germany	1989–1990	<0.03–10 µg/litre	Wittsiepe, 1990
Sediment	Japan	1976	<0.05 µg/g, <1 µg/g	Environment Agency Japan, 1976

^a Detection limit not specified.

Table 2: Concentrations of limonene in various media.

Medium	Concentration	Location and sampling date	Reference
Air, rural	0.036 µg/m ³ (6.4×10 ⁻³ ppb)	Whitaker's Forest, Sierra Nevada Mountains, California, June 1990	Helmig & Arey, 1992
	0.34 µg/m ³ (6.0×10 ⁻² ppb)	Eastern Germany, July (forest site)	Ciccoioli et al., 1993
	0.1–2.2 ppb (0.6–12.2 µg/m ³)	Forest, Northwest Quebec, Canada, July 1989	Clement et al., 1990
Air, urban/suburban	nd ^b –0.36 µg/m ³ (nd–6.4×10 ⁻² ppb)	Urban Riverside, California, June 1990	Helmig & Arey, 1992
	0.14 ng/litre (2.5×10 ⁻² ppb)	Montelibretti, Italy (suburban site)	Ciccoioli et al., 1992
Air, emissions	1.7–10 100 µg/m ³ (0.3–1.8×10 ³ ppb)	8 municipal solid waste composting facilities, USA	Eitzer, 1995
	1.9–14 µg/m ³ (0.34–2.5 ppb)	Emission plumes from kraft pulp industries, Sweden	Strömvall, 1992
Water, sea	2–40 ng/litre	Gulf of Mexico, ^d 1977	Sauer, 1981
	0.55 ng/litre (mean)	Barcelona, Mediterranean Sea, Spain, 1986	Gomez-Belinchon et al., 1991
Water, river	590 ng/litre (mean)	Llobregat River, Barcelona, Spain, 1985–1986	Gomez-Belinchon et al., 1991
	1600 ng/litre (mean)	Besós River, Barcelona, Spain, 1985–1986	Gomez-Belinchon et al., 1991
Water, estuary	25–633 ng/litre	Southampton Water estuary, UK	Bianchi et al., 1991
Water, groundwater	70 ng/litre (max.)	Otis Air Base, Massachusetts (sewage-contaminated water)	Barber et al., 1988
	1–130 µg/litre	Former site for production of charcoal and pine tar products, Gainesville, Florida	McCreary et al., 1983
Water, wastewater	nd–20 µg/litre	Influent waste water, sewage works, Göteborg, Sweden, 1989–1991	Paxéus et al., 1992
	10–220 ppb (10×10 ³ – 220×10 ³ ng/litre)	Kraft mill aerated lagoons, USA	Wilson & Hrutfiord, 1975
Sediment	105–807 ng/kg	Southampton Water estuary, UK	Bianchi et al., 1991
Soil	nd–920 µg/g	Former site for production of charcoal and pine tar products, Gainesville, Florida, USA	McCreary et al., 1983

Table 3: Investigations of non-neoplastic effects of 1,1,2,2-tetrachloroethane.

Study design	Effects	Effect level	Comments	Reference
INHALATION				
Male rats exposed to 50 mg/m ³ , 4 hours/day, 5 days/week, for 5 weeks; or to 130 mg/m ³ for 15 minutes, 5 times/day, separated by 40-minute intervals, for 5 weeks	Neurological effects; alterations in biochemical parameters and organ weights (although within ranges observed in controls); no "morphological changes"	Effects at 50 mg/m ³	Strain and number of rats not specified; nature and extent of histopathological examination not specified	Schmidt et al., 1975
Fifty-five female Sprague-Dawley rats exposed to 560 ml/m ³ for 5 or 6 hours/day, 5 days/week, for 15 weeks; liver, kidneys, lungs, ovaries, uterus, and adrenal glands histopathologically examined	Transient increase in hepatic DNA synthesis, reversible histopathological changes in the liver; increase in relative liver weight	Effects at 560 ml/m ³ (equivalent to 130 ppm or 907 mg/m ³ , based on ATSDR [1994] conversion)	One exposure group only; uncertainty concerning exposure level based on unclear information in article (note: concentration more than approximately 10-fold higher than that at which effects were reported in other studies, no matter how converted)	Truffert et al., 1977
INGESTION				
Groups of 10 rats administered 3.2, 8.0, 20, or 50 mg/kg body weight per day by gavage for 2–150 days	Damage to liver, kidney, testicles, and thyroid gland (determined by histological, enzyme histochemical, and histoautoradiographic techniques)	Effects at 3.2 mg/kg body weight per day	Inadequate documentation of protocol and results; no quantitative data; not reported in which dose groups effects were observed (some groups were also concomitantly exposed to high temperatures); not possible to verify effect level	Gohlke et al., 1977
Five male or female B6C3F ₁ mice administered 0, 32, 56, 100, 178, or 316 mg/kg body weight per day by gavage, 5 days/week, for 6 weeks, followed by 2 weeks of observation	No effects on body weight gain or mortality	No effects at highest dose of 316 mg/kg body weight per day	No end-points other than body weight and mortality appear to have been examined	NCI, 1978
Five male or female Osborne-Mendel rats administered 0, 56, 100, 178, 316, or 562 mg/kg body weight per day by gavage, 5 days/week, for 6 weeks, followed by 2 weeks of observation	Decrease in body weight gain in males at 178 mg/kg body weight per day and in females at 100 and 178 mg/kg body weight per day; all females exposed to 316 mg/kg body weight per day died; one male exposed to 100 mg/kg body weight per day died	Effects at 100 mg/kg body weight per day; no effects at 56 mg/kg body weight per day	No end-points other than body weight and mortality appear to have been examined; no data presented on effects on body weight gain at two highest doses or on mortality for other dose groups	NCI, 1978

Table 4: Genotoxicity of 1,1,2,2-tetrachloroethane *in vitro*.

Species (test system)	End-point	Result		Reference
		With activation	Without activation	
Saccharomyces cerevisiae D7	Mitotic gene conversion	nt	+	Callen et al., 1980
Saccharomyces cerevisiae D7 XV185-14C	Recombination	nt	+	Nestmann and Lee, 1983
	Gene conversion and reversion	nt	–	
		nt	–	
Salmonella typhimurium TA1530	Reverse mutations	nt	+	Brem et al., 1974
TA1535		nt	+	
TA1538		nt	–	
Salmonella typhimurium TA100		–	–	
Salmonella typhimurium BA13/BAL13	Forward mutations	–	–	Warner et al., 1988 Roldan-Arjona et al., 1991
Escherichia coli (polymerase deficient pol A ⁺ /pol A ⁻)	DNA damage	nt	+	Brem et al., 1974
Escherichia coli PQ37	Gene mutation	–	–	Mersch-Sundermann et al., 1989b
Escherichia coli	Induction of prophage lambda	+	–	DeMarini & Brooks, 1992
Aspergillus nidulans	Mitotic malsegregation	nt	+	Crebelli et al., 1988
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Galloway et al., 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Galloway et al., 1987
BALB/c3T3 cells (mouse)	Sister chromatid exchange	+	+	Colacci et al., 1992
Mouse hepatocytes	DNA growth, repair, or synthesis	nt	–	Williams, 1983
Mouse hepatocytes	DNA repair	nt	–	Milman et al., 1988
Rat hepatocytes	DNA growth, repair, or synthesis	nt	–	Williams, 1983
Rat hepatocytes	DNA repair	nt	–	Milman et al., 1988
Human embryonic intestinal cells	Unscheduled DNA synthesis	–	–	McGregor, 1980

nt = not tested

Table 5: Cross-sectional epidemiological studies — respiratory effects

Protocol	Results	Reference
Study population composed of 40 workers from two factories who were exposed to methyl methacrylate for >5 years and 45 controls engaged in similar job categories but without exposure to methyl methacrylate. Mean atmospheric concentrations of methyl methacrylate at the two factories were 18.5 ppm (75.8 mg/m ³) (range 9–32 ppm [36.9–131.1 mg/m ³]) and 21.6 ppm (88.6 mg/m ³) (range 11.9–38.5 ppm [48.8–157.9 mg/m ³]). Smoking history and information on the presence of respiratory symptoms were gathered by means of a questionnaire. Respiratory measurements (maximum expiratory flow volume [MEFV], forced vital capacity [FVC], forced expiratory volume [FEV]) were performed by means of a spirometer: one before the working shift, and the second in the last 2 hours of the 8-hour shift.	An increase in the prevalence of chronic cough was observed in exposed workers compared with controls (p = 0.04). This difference remained significant after adjustment for smoking (p = 0.03). Airway resistance increased during the 8-hour work shift in workers exposed to methyl methacrylate (as measured by MEF ₅₀ (p = 0.04) and MEF ₅₀ /MEF (p = 0.01). The obstruction was mild, and forced expiratory volume in one second (FEV ₁) did not decrease during the work shift.	Marez et al., 1993
Ninety-one exposed and 43 non-exposed workers were evaluated at five plants manufacturing polymethyl methacrylate sheets. For exposed workers, 8-hour time-weighted-average concentrations of methyl methacrylate were between 4 and 49 ppm (16.4–200.9 mg/m ³). Evaluation of chronic effects was conducted through an extensive questionnaire, a comparison of mean blood pressure values with predicted values from the 1971–1972 US National Health Survey, and results of pulmonary function tests, haemoglobin and white blood cell counts, urinalysis, and blood chemistry.	No significant differences were observed for respiratory function, chronic liver and gastrointestinal effects, skin and allergic problems, blood pressure and pulse rate, white blood cell count, and haemoglobin values. The only parameters for which effects were observed were serum glucose, blood urea nitrogen, cholesterol, albumin, and total bilirubin values, although the implication of these effects remains unclear. Although not statistically significant, the data also “suggested possible alterations in skin and nervous system symptomatology, urinalysis findings, and serum triglycerides.”	Cromer & Kronoveter, 1976