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Concise International Chemical Assessment Document 40

FORMALDEHYDE

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

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

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour 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. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

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

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

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

provided as guidance only. The reader is referred to EHC 170¹ for advice on the derivation of health-based guidance values.

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

Procedures

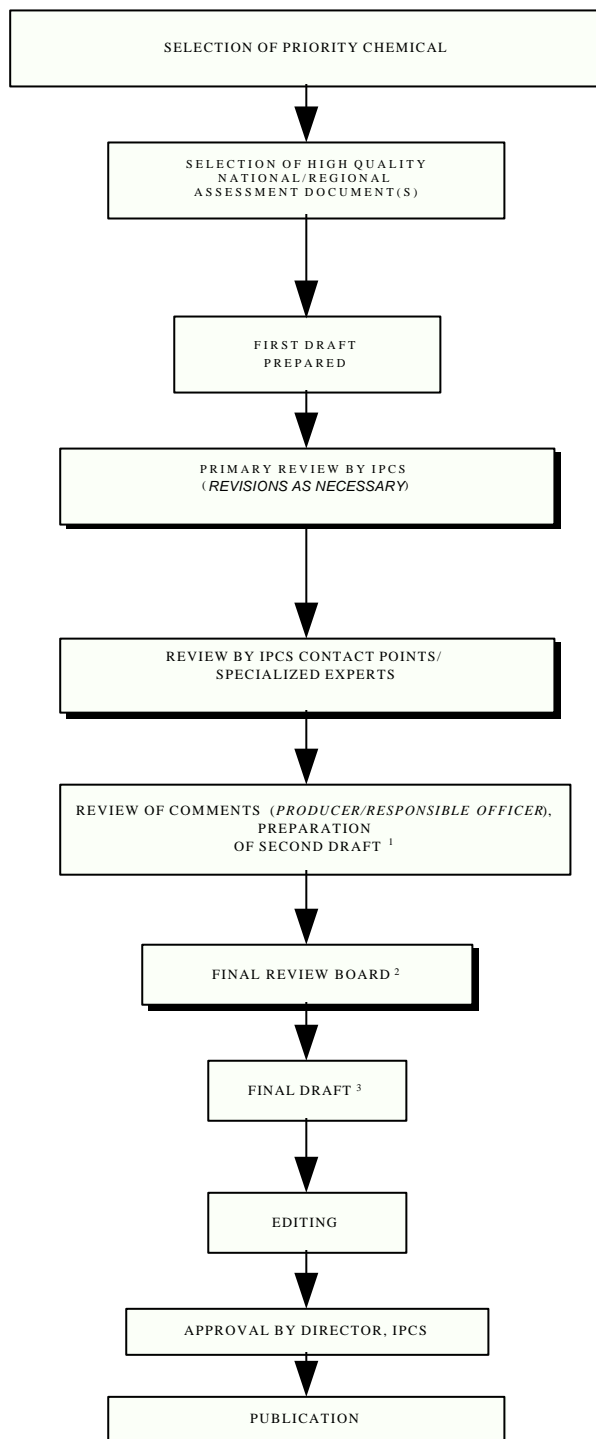
The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, 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 and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

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

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

CICAD PREPARATION FLOW CHART



¹ Taking into account the comments from reviewers.

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

³ Includes any revisions requested by the Final Review Board.

is submitted to a Final Review Board together with the reviewers' comments.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

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

This CICAD on formaldehyde was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Branch of Environment Canada based on documentation prepared as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of assessments on Priority Substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. This CICAD additionally includes information on occupational exposure. Data identified as of the end of December 1999 (environmental effects) and January 1999 (human health effects) were considered in this review.¹ Other reviews that were also consulted include IARC (1981, 1995), IPCS (1989), RIVM (1992), BIBRA Toxicology International (1994), and ATSDR (1999). Information on the nature of the peer review and availability of the source document (Environment Canada & Health Canada, 2001) and its supporting documentation is presented in Appendix 1. It should be noted, as indicated therein, that the biologically motivated case-specific model for exposure–response analyses for cancer included in this CICAD was the product of a joint effort involving the US Environmental Protection Agency (EPA), Health Canada, the Chemical Industry Institute of Toxicology (CIIT), and others. The product of this collaborative effort superseded the content of a draft CICAD on formaldehyde prepared previously by the Office of Pollution Prevention and Toxics of the US EPA, on the basis of health-related toxicological information published prior to 1992. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Geneva, Switzerland, on 8–12 January 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card for formaldehyde (ICSC 0275), produced by the International Programme on Chemical Safety (IPCS, 2000), has also been reproduced in this document.

¹ New information flagged by reviewers and obtained in a literature search conducted prior to the Final Review Board meeting has been scoped to indicate its likely impact on the essential conclusions of this assessment, primarily to establish priority for its consideration in an update. More recent information not critical to the hazard characterization or exposure–response analysis, considered by reviewers to add to informational content, has been included.

Formaldehyde (CAS No. 50-0-0) is a colourless, highly flammable gas that is sold commercially as 30–50% (by weight) aqueous solutions. Formaldehyde enters the environment from natural sources (including forest fires) and from direct human sources, such as automotive and other fuel combustion and industrial on-site uses. Secondary formation also occurs, by the oxidation of natural and anthropogenic organic compounds present in air. The highest concentrations measured in the environment occur near anthropogenic sources; these are of prime concern for the exposure of humans and other biota. Motor vehicles are the largest direct human source of formaldehyde in the environment of the source country (Canada). Releases from industrial processes are considerably less. Industrial uses of formaldehyde include the production of resins and fertilizers.

When formaldehyde is released to or formed in air, most of it degrades, and a very small amount moves into water. When formaldehyde is released into water, it does not move into other media but is broken down. Formaldehyde does not persist in the environment, but its continuous release and formation result in long-term exposure near sources of release and formation.

The focus of the human health assessment is airborne exposure, due primarily to the lack of representative data on concentrations in media other than air and limited data on effects following ingestion.

Extensive recent data are available for concentrations of formaldehyde in air at industrial, urban, suburban, rural, and remote locations in the source country (Canada). There are fewer but still considerable data on concentrations in indoor air, which are higher. Data on concentrations in water are more limited. Although formaldehyde is a natural component of a variety of foodstuffs, monitoring has generally been sporadic and source directed. Based on available data, the highest concentrations of formaldehyde occurring naturally in foods are in some fruits and marine fish. Formaldehyde may also be present in food due to its use as a bacteriostatic agent in production and its addition to animal feed to improve handling characteristics. Formaldehyde and formaldehyde derivatives are also present in a wide variety of consumer products to protect the products from spoilage by microbial contamination. The general population is also exposed during release from combustion (e.g., from cigarettes and cooking) and emission from some building materials, such as pressed wood products.

Since formaldehyde (also a product of intermediary metabolism) is water soluble, highly reactive with biological macromolecules, and rapidly metabolized, adverse effects resulting from exposure are observed primarily in those tissues or organs with which formaldehyde first comes into contact (i.e., the respiratory and aerodigestive tract, including oral and gastrointestinal mucosa, following inhalation or ingestion, respectively).

Sensory irritation of the eyes and respiratory tract by formaldehyde has been observed consistently in clinical studies and epidemiological surveys in occupational and residential environments. At concentrations higher than those generally associated with sensory irritation, formaldehyde may also contribute to the induction of generally small, reversible effects on lung function.

For the general population, dermal exposure to concentrations of formaldehyde, in solution, in the vicinity of 1–2% (10 000–20 000 mg/litre) is likely to cause skin irritation; however, in hypersensitive individuals, contact dermatitis can occur following exposure to formaldehyde at concentrations as low as 0.003% (30 mg/litre). In North America, less than 10% of patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde. Although it has been suggested in case reports for some individuals that formaldehyde-induced asthma was attributable to immunological mechanisms, no clear evidence has been identified. However, in studies with laboratory animals, formaldehyde has enhanced their sensitization to inhaled allergens.

Following inhalation in laboratory animals, formaldehyde causes degenerative non-neoplastic effects in mice and monkeys and nasal tumours in rats. *In vitro*, formaldehyde induced DNA–protein crosslinks, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, and gene mutations in human and rodent cells. Formaldehyde administered by inhalation or gavage to rats *in vivo* induced chromosomal anomalies in lung cells and micronuclei in the gastrointestinal mucosa. The results of epidemiological studies in occupationally exposed populations are consistent with a pattern of weak positive responses for genotoxicity, with good evidence of an effect at site of contact (e.g., micronucleated buccal or nasal mucosal cells). Evidence for distal (i.e., systemic) effects is equivocal. Overall, based on studies in both animals and humans, formaldehyde is weakly genotoxic, with good evidence of an effect at site of contact, but less convincing evidence at distal sites. Epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde exposure and human

cancer, although the possibility of increased risk of respiratory cancers, particularly those of the upper respiratory tract, cannot be excluded on the basis of available data. Therefore, based primarily upon data derived from laboratory studies, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans.

The majority of the general population is exposed to airborne concentrations of formaldehyde less than those associated with sensory irritation (i.e., 0.083 ppm [0.1 mg/m³]). However, in some indoor locations, concentrations may approach those associated with eye and respiratory tract sensory irritation in humans. Risks of cancer estimated on the basis of a biologically motivated case-specific model for calculated exposure of the general population to formaldehyde in air based on the sample exposure scenario for the source country (Canada) are exceedingly low. This model incorporates two-stage clonal growth modelling and is supported by dosimetry calculations from computational fluid dynamics modelling of formaldehyde flux in various regions of the nose and single-path modelling for the lower respiratory tract.

Environmental toxicity data are available for a wide range of terrestrial and aquatic organisms. Based on the maximum concentrations measured in air, surface water, effluents, and groundwater in the sample exposure scenario from the source country and on the estimated no-effects values derived from experimental data for terrestrial and aquatic biota, formaldehyde is not likely to cause adverse effects on terrestrial or aquatic organisms.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Formaldehyde (CH₂O) is also known as methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane, and formic aldehyde. Its Chemical Abstracts Service (CAS) registry number is 50-00-0.

At room temperature, formaldehyde is a colourless gas with a pungent, irritating odour. It is highly reactive, readily undergoes polymerization, is highly flammable, and can form explosive mixtures in air. It decomposes at temperatures above 150 °C. Formaldehyde is readily soluble in water, alcohols, and other polar solvents. In aqueous solutions, formaldehyde hydrates and polymerizes and can exist as methylene glycol, polyoxymethylene, and hemiformals. Solutions with high

concentrations (>30%) of formaldehyde become turbid as the polymer precipitates (IPCS, 1989). As a reactive aldehyde, formaldehyde can undergo a number of self-association reactions, and it can associate with water to form a variety of chemical species with properties different from those of the pure monomolecular substance. These associations tend to be most prevalent at high concentrations of formaldehyde; hence, data on properties at high concentrations are not relevant to dilute conditions.

Values reported for the physical and chemical properties of formaldehyde are given in Table 1. Additional physical/chemical properties are presented in the International Chemical Safety Card reproduced in this document.

Table 1: Physical and chemical properties of formaldehyde reported in literature.^a

Property	Range of reported values ^b
Relative molecular mass	30.03
Melting point (°C)	! 118 to ! 92
Boiling point (°C, at 101.3 kPa)	! 21 to ! 19
Vapour pressure (calculated) (Pa, at 25 °C)	516 000
Water solubility (mg/litre, at 25 °C) ^c	400 000 to 550 000
Henry's law constant (Pa@m ³ /mol, at 25 °C)	2.2×10^{-2} to 3.4×10^{-2}
Log octanol/water partition coefficient (log K_{ow})	! 0.75 to 0.35
Log organic carbon/water partition coefficient (log K_{oc})	0.70 to 1.57
Conversion factor	1 ppm = 1.2 mg/m ³

^a Because of polymerization and other reactions, care should be taken in interpreting or using reported values. See also text.

^b Includes experimental and calculated values from Hansch & Leo (1979, 1981); Karickhoff et al. (1979); Kenaga & Goring (1980); Weast (1982–1983); Verschueren (1983); Perry & Green (1984); Dean (1985); US EPA (1985); Betterton & Hoffmann (1988); Deneer et al. (1988); Howard (1989); Sangster (1989); Zhou & Mopper (1990); Mackay et al. (1995); Staudinger & Roberts (1996).

^c Water solubility of a chemical is defined as the maximum amount of the chemical that will dissolve in water at a specified temperature, pressure, and pH. Results such as 1 220 000 mg/litre (Dean, 1985) and 1.0×10^8 mg/litre (DMER & AEL, 1996) have been quoted. These values are pseudo-solubilities, since solutions become turbid as the polymer precipitates at concentrations of approximately 55% and greater.

Pure formaldehyde is not available commercially but is sold as 30–50% (by weight) aqueous solutions. Formalin (37% CH₂O) is the most common solution. Methanol or other substances are usually added to the solution as stabilizers to reduce the intrinsic polymerization of formaldehyde (IPCS, 1989; Environment Canada, 1995). In solid form, formaldehyde is marketed as trioxane [(CH₂O)₃] and its polymer paraformaldehyde, with 8–100 units of formaldehyde (IPCS, 1989).

3. ANALYTICAL METHODS

Selected methods for the determination of formaldehyde in air, food, and wood are presented in Table 2 (IARC, 1995). The most widely used methods for the detection of formaldehyde are based on spectrophotometry, but other methods, such as colorimetry, fluorimetry, high-performance liquid chromatography, polarography, gas chromatography, infrared detection, and gas detector tubes, are also used. Organic and inorganic chemicals, such as sulfur dioxide and other aldehydes and amines, can interfere with these methods of detection. The most sensitive of these methods is flow injection (Fan & Dasgupta, 1994), which has a detection limit of 9 ppt (0.011 µg/m³). Another commonly used method is high-performance liquid chromatography, which offers a detection limit of 0.0017 ppm (0.002 mg/m³) (IARC, 1995). Gas detector tubes and infrared analysers are often used for monitoring workplace atmospheres and have a sensitivity of about 0.33–0.42 ppm (0.4–0.5 mg/m³) (IARC, 1995).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Data on sources and emissions primarily from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as an example. Sources and patterns of emissions in other countries are expected to be similar, although quantitative values may vary.

Formaldehyde is formed primarily by the combustion of organic materials and by a variety of natural and anthropogenic activities. Secondary formation of formaldehyde occurs in the atmosphere through the oxidation of natural and anthropogenic volatile organic compounds (VOCs) in the air. While there are no reliable

Table 2: Methods for the analysis of formaldehyde in air and food.^{a,b}

Sample matrix/preparation	Assay procedure	Limit of detection	Reference
Air			
Draw air through an impinger containing aqueous pararosaniline and sodium sulfite.	S	0.0083 ppm (0.01 mg/m ³)	Georghiou et al., 1993
Draw air through PTFE filter and impingers, each treated with sodium bisulfite solution; develop colour with chromotropic acid and sulfuric acid; read absorbance at 580 nm.	S	0.025 ppm (0.03 mg/m ³)	Eller, 1989a
Draw air through solid sorbent tube treated with 10% 2-(hydroxymethyl) piperidine on XAD-2; desorb with toluene.	GC/FID	0.25 ppm (0.3 mg/m ³)	Eller, 1989b
	GC/NSD	0.017 ppm (0.02 mg/m ³)	US OSHA, 1990
Draw air through tube that contains a smaller concentric tube made of Nafion (semipermeable) through which water flows in the opposite direction and serves to trap formaldehyde; add 1,3-cyclohexanedione in acidified ammonium acetate to form dihydropyridine derivative in flow injection analysis system.	Fluorescence (FIA)	9 ppt (0.011 µg/m ³)	Fan & Dasgupta, 1994
Draw air through impinger containing hydrochloric acid/2,4-dinitrophenylhydrazine reagent and isooctane; extract with hexane/dichloromethane.	HPLC/UV	0.0017 ppm (0.002 mg/m ³)	US EPA, 1988a
Draw air through silica gel coated with acidified 2,4-dinitrophenylhydrazine reagent.	HPLC/UV	0.0017 ppm (0.002 mg/m ³)	US EPA, 1988b
Expose passive monitor (Du Pont Pro-Tek Formaldehyde Badge) for at least 2 ppm-h. Analyse according to manufacturer's specifications.	Chromotropic acid test	0.083 ppm (0.1 mg/m ³)	Kennedy & Hull, 1986; Stewart et al., 1987
Food			
Distil sample; add 1,8-dihydroxynaphthalene-3,6-disulfonic acid in sulfuric acid; purple colour indicates presence of formaldehyde.	Chromotropic acid test	NR	Helrich, 1990
Distil sample; add to cold sulfuric acid; add aldehyde-free milk; add bromine hydrate solution; purplish-pink colour indicates presence of formaldehyde.	Hehner-Fulton test	NR	Helrich, 1990
Wood			
Large-scale chamber tests.		0.083 ppm (0.1 mg/m ³)	European Commission, 1989; ASTM, 1990; Groah et al., 1991; Jann, 1991
Formaldehyde, absorbed in distilled water, reacts specifically with a chromotropic acid-sulfuric acid solution.	2-h desiccator test	NR	National Particleboard Association, 1983; Groah et al., 1991
Small samples are boiled in toluene, and the formaldehyde-laden toluene is distilled through distilled/deionized water, which absorbs the formaldehyde; a sample of the water is then analysed photometrically by the acetylacetone or pararosaniline method.	Perforator method	NR	British Standards Institution, 1989
Formaldehyde in water is determined by adding sulfuric acid solution and an excess of iodine; the iodine oxidizes the formaldehyde, and the excess is back-titrated with sodium thiosulfate.	Iodometric method	NR	British Standards Institution, 1989

^a From IARC (1995).

^b Abbreviations used: GC/FID = gas chromatography/flame ionization detection; GC/NSD = gas chromatography/nitrogen selective detection; FIA = fluorescence immunoassay; HPLC/UV = high-performance liquid chromatography/ultraviolet detection; NR = not reported; PTFE = polytetrafluoroethylene; S = spectrometry.

estimates for releases from natural sources and for secondary formation, these may be expected to be much larger than direct emissions from anthropogenic activities. However, highest concentrations have been measured near key anthropogenic sources, such as automotive and industrial emissions (see section 6.1.1).

4.1 Natural sources

Formaldehyde occurs naturally in the environment and is the product of many natural processes. It is released during biomass combustion, such as forest and brush fires (Howard, 1989; Reinhardt, 1991). In water, it is also formed by the irradiation of humic substances by sunlight (Kieber et al., 1990).

As a metabolic intermediate, formaldehyde is present at low levels in most living organisms (IPCS, 1989; IARC, 1995). It is emitted by bacteria, algae, plankton, and vegetation (Hellebust, 1974; Zimmermann et al., 1978; Eberhardt & Sieburth, 1985; Yamada & Matsui, 1992; Nuccio et al., 1995).

4.2 Anthropogenic sources

Anthropogenic sources of formaldehyde include direct sources such as fuel combustion, industrial on-site uses, and off-gassing from building materials and consumer products.

Although formaldehyde is not present in gasoline, it is a product of incomplete combustion and is released, as a result, from internal combustion engines. The amount generated depends primarily on the composition of the fuel, the type of engine, the emission control applied, the operating temperature, and the age and state of repair of the vehicle. Therefore, emission rates are variable (Environment Canada, 1999a).

Based on data for 1997 reported to the National Pollutant Release Inventory, on-road motor vehicles are the largest direct source of formaldehyde released into the Canadian environment. Data on releases from on-road vehicles were estimated by modelling (Mobile 5C model), based on assumptions outlined in Environment Canada (1996). The amount estimated by modelling to have been released in 1997 from on-road motor vehicles was 11 284 tonnes (Environment Canada, 1999b). While Environment Canada (1999b) did not distinguish between gasoline-powered and diesel-powered vehicles, it has been estimated, based on emissions data from these vehicles, that they account for about 40% and 60% of on-road automotive releases, respectively. Aircraft emitted an estimated 1730 tonnes, and the marine sector released about 1175 tonnes (Environment Canada, 1999b). It can be expected that the rates of release of

formaldehyde from automotive sources have changed and will continue to change; many current and planned modifications to automotive emission control technology and gasoline quality would lead to decreases in the releases of formaldehyde and other VOCs (Environment Canada, 1999b).

Other anthropogenic combustion sources (covering a range of fuels from wood to plastics) include wood-burning stoves, fireplaces, furnaces, power plants, agricultural burns, waste incinerators, cigarette smoking, and the cooking of food (Jermini et al., 1976; Kitchens et al., 1976; Klus & Kuhn, 1982; Ramdahl et al., 1982; Schriever et al., 1983; Lipari et al., 1984; IPCS, 1989; Walker & Cooper, 1992; Baker, 1994; Guski & Raczynski, 1994). Cigarette smoking in Canada is estimated to produce less than 84 tonnes per year, based on estimated emission rates (IPCS, 1989) and a consumption rate of approximately 50 billion cigarettes per year (Health Canada, 1997). Canadian coal-based electricity generating plants are estimated to emit 0.7–23 tonnes per year, based on US emission factors (Lipari et al., 1984; Sverdrup et al., 1994), the high heating value of fuel, and Canadian coal consumption in 1995 (D. Rose, personal communication, 1998). A gross estimate of formaldehyde emissions from municipal, hazardous, and biomedical waste in Canada is 10.6 tonnes per year, based on measured emission rates from one municipal incinerator in Ontario (Novamann International, 1997; Environment Canada, 1999a).

Industrial releases of formaldehyde can occur at any stage during the production, use, storage, transport, or disposal of products with residual formaldehyde. Formaldehyde has been detected in emissions from chemical manufacturing plants (Environment Canada, 1997b,c, 1999a), pulp and paper mills, forestry product plants (US EPA, 1990; Fisher et al., 1991; Environment Canada, 1997b, 1999a; O'Connor & Voss, 1997), tire and rubber plants (Environment Canada, 1997a), petroleum refining and coal processing plants (IARC, 1981; US EPA, 1993), textile mills, automotive manufacturing plants, and the metal products industry (Environment Canada, 1999a).

Total environmental releases in Canada from 101 facilities were 1423.9 tonnes in 1997, with reported releases to different media as follows: 1339.3 tonnes to air, 60.5 tonnes to deep-well injection, 19.4 tonnes to surface water, and 0 tonnes to soil. From 1979 to 1989, about 77 tonnes were spilled in Canada as a result of 35 reported incidents. Releases of formaldehyde to groundwater from embalming fluids in bodies buried in cemeteries are expected to be very small based on groundwater samples and the estimated loading rates of six cemeteries in Ontario (Chan et al., 1992). In the USA

in 1992, total releases of formaldehyde to environmental media from certain types of US industries were approximately 8960 tonnes, of which approximately 58%, 39%, 2%, and 1% were released to the atmosphere, to underground injection sites, to surface water, and to land, respectively (TRI, 1994).

Formaldehyde has been detected in the off-gassing of formaldehyde products such as wood panels, latex paints, new carpets, textile products, and resins. While emission rates have been estimated for some of these sources, there are insufficient data for estimating total releases (Little et al., 1994; NCASI, 1994; Environment Canada, 1995). In some countries, there have been regulatory and voluntary initiatives to control emissions from building materials and furnishings, since these are recognized as the major sources of elevated concentrations of formaldehyde in indoor air.

4.3 Secondary formation

Formaldehyde is formed in the troposphere by the photochemical oxidation of many types of organic compounds, including naturally occurring compounds, such as methane (IPCS, 1989; US EPA, 1993) and isoprene (Tanner et al., 1994), and pollutants from mobile and stationary sources, such as alkanes, alkenes (e.g., ethene, propene), aldehydes (e.g., acetaldehyde, acrolein), and alcohols (e.g., allyl alcohol, methanol, ethanol) (US EPA, 1985; Atkinson et al., 1989, 1993; Grosjean, 1990a,b, 1991a,b,c; Skov et al., 1992; Grosjean et al., 1993a,b, 1996a,b; Bierbach et al., 1994; Kao, 1994).

Given the diversity and abundance of formaldehyde precursors in urban air, secondary atmospheric formation frequently exceeds direct emissions from combustion sources, especially during photochemical air pollution episodes, and it may contribute up to 70–90% of the total atmospheric formaldehyde (Grosjean, 1982; Grosjean et al., 1983; Lowe & Schmidt, 1983). In California, USA, Harley & Cass (1994) estimated that photochemical formation was more important than direct emissions in Los Angeles during the summertime days studied; in winter or at night and in the early morning, direct emissions can be more important. This was also observed in Japan, where the concentrations of formaldehyde in the central mountainous region were not associated directly with motor exhaust but rather were associated with the photochemical oxidation of anthropogenic pollutants occurring there through long-range transport (Satsumabayashi et al., 1995).

4.4 Production and use

Formaldehyde is produced commercially from methanol. The primary methanol oxidation processes use metal catalyst (silver now, previously copper) or metal

oxide catalyst (ATSDR, 1999). Similar methods of production are used in many countries worldwide. Table 3 shows the production of formaldehyde by selected countries, with the highest amounts originating from the USA and Japan.

In 1996, the domestic production of formaldehyde in Canada was approximately 222 000 tonnes (Environment Canada, 1997bc); in 1994, domestic production in the USA was 3.6 million tonnes (Kirschner, 1995). The production of formaldehyde worldwide in 1992 was estimated at approximately 12 million tonnes (IARC, 1995).

Total Canadian domestic consumption of formaldehyde was reported at about 191 000 tonnes for 1996 (Environment Canada, 1997b). Formaldehyde is used predominantly in the synthesis of resins, with urea-formaldehyde (UF) resins, phenolic-formaldehyde resins, pentaerythritol, and other resins accounting for about 92% of Canadian consumption. About 6% of uses were

Table 3: Production of formaldehyde in selected countries.^a

Country or region	Production (kilotonnes) ^b		
	1982	1986	1990
Brazil	152	226	N/A
Canada	70	117	106
China	286	426	467
Former Czechoslovakia	254	274	N/A
Denmark	N/A	3	0.3
Finland	N/A	5	48
France	79	80	100
Germany	630	714	680
Hungary	13	11	N/A
Italy	125	135	114
Japan	N/A	1188	1460
Mexico	83	93	N/A
Poland	219	154	N/A
Portugal	N/A	70	N/A
Republic of Korea	N/A	122	N/A
Spain	N/A	91	136
Sweden	N/A	223	244
Taiwan	N/A	204	215
Turkey	N/A	21	N/A
United Kingdom	107	103	80
USA ^c	2185	2517	3048
Former Yugoslavia	108	99	88

^a From IARC (1995).

^b N/A = not available.

^c 37% by weight.

related to fertilizer production, while 2% of the formaldehyde was used for various other purposes, such as preservatives and disinfectants (Environment Canada, 1997b). Formaldehyde can be used in a variety of industries, including the medical, detergent, cosmetic, food, rubber, fertilizer, metal, wood, leather, petroleum, and agricultural industries (IPCS, 1989), and as a hydrogen sulfide scavenger in oil operations (Tiemstra, 1989).

Formaldehyde is often added to cosmetics, in which it acts as a preservative and an antimicrobial agent. Its use in cosmetics is regulated or voluntarily restricted. In Canada, for example, formaldehyde is acceptable for use in non-aerosol cosmetics, provided the concentration does not exceed 0.2% (R. Green, personal communication, 1994). It is also included in the Cosmetic Notification Hot List, with the recommendation to limit its concentration in cosmetics to less than 0.3%, except for fingernail hardeners, for which a maximum concentration of 5% applies (A. Richardson, personal communication, 1999).

In the agriculture industry, formaldehyde has been used as a fumigant, as a preventative for mildew and spelt in wheat, and for rot in oats. It has also been used as a germicide and fungicide for plants and vegetables and as an insecticide for destroying flies and other insects. In Canada, formaldehyde is registered as a pesticide under the *Pest Control Products Act*; about 131 tonnes are applied annually for pest control. Approximately 80% of the slow-release fertilizer market is based on UF-containing products (ATSDR, 1999; HSDB, 1999). In Canada, there are currently 59 pest control products containing formaldehyde registered with the Pest Management Regulatory Agency. Formaldehyde is present as a formulant in 56 of these products, at concentrations ranging from 0.02% to 1% by weight. Formaldehyde is an active ingredient in the remaining three products, at concentrations ranging from 2.3% to 37% in the commercially available products (G. Moore, personal communication, 2000).

Formaldehyde is also used as an antibacterial agent in processing of foodstuffs. For example, the *Food and Drugs Act* allows up to 2 ppm (i.e., 2 mg/kg) formaldehyde in maple syrup resulting from the use of paraformaldehyde to deter bacterial growth in the tap holes of maple trees in Canada (M. Feeley, personal communication, 1996). Formaldehyde is also registered as a feed under the *Feed Act* in Canada.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

The sections below summarize the available information on the distribution and fate of formaldehyde released into the environment. More detailed fate information is provided in Environment Canada (1999a).

5.1 Air

Formaldehyde emitted to air primarily reacts with photochemically generated hydroxyl radicals in the troposphere or undergoes direct photolysis (Howard et al., 1991; US EPA, 1993). Minor processes include reactions with nitrate radicals, hydroperoxyl radicals, hydrogen peroxide, ozone, and chlorine (US EPA, 1993). Small amounts of formaldehyde may also transfer into rain, fog, and clouds or be removed by dry deposition (Warneck et al., 1978; Zafiriou et al., 1980; Howard, 1989; Atkinson et al., 1990; US EPA, 1993).

Reaction with the hydroxyl radical is considered to be the most important photooxidation process, based on the rate constants and the concentrations of the reactants (Howard et al., 1991; US EPA, 1993). Factors influencing the atmospheric lifetime of formaldehyde, such as time of day, intensity of sunlight, temperature, etc., are mainly those affecting the availability of hydroxyl and nitrate radicals (US EPA, 1993). The atmospheric half-life of formaldehyde, based on hydroxyl radical reaction rate constants, is calculated to be between 7.1 and 71.3 h (Atkinson, 1985; Atkinson et al., 1990). Products that can be formed from hydroxyl radical reaction include water, formic acid, carbon monoxide, and the hydroperoxyl/formaldehyde adduct (Atkinson et al., 1990).

Photolysis can take two pathways. The dominant pathway produces stable molecular hydrogen and carbon monoxide. The other pathway produces the formyl radical and a hydrogen atom (Lowe et al., 1980), which react quickly with oxygen to form the hydroperoxyl radical and carbon monoxide. Under many conditions, the radicals from photolysis of formaldehyde are the most important net source of smog generation (US EPA, 1993). When the rates of these reactions are combined with estimates of actinic radiance, the estimated half-life of formaldehyde due to photolysis is 1.6 h in the lower troposphere at a solar zenith angle of 40° (Calvert et al., 1972). A half-life of 6 h was measured based on simulated sunlight (Lowe et al., 1980).

The nighttime destruction of formaldehyde is expected to occur by the gas-phase reaction with nitrate radicals (US NRC, 1981); this tends to be more significant in urban areas, where the concentration of the

nitrate radical is higher than in rural areas (Altshuller & Cohen, 1964; Gay & Bufalini, 1971; Maldotti et al., 1980). A half-life of 160 days was calculated using an average atmospheric nitrate radical concentration typical of a mildly polluted urban centre (Atkinson et al., 1990), while a half-life of 77 days was estimated based on measured rate constants (Atkinson et al., 1993). Nitric acid and formyl radical have been identified as products of this reaction. They react rapidly with atmospheric oxygen to produce carbon monoxide and hydroperoxyl radicals, which can react with formaldehyde to form formic acid. However, because of this rapid back-reaction, the reaction of nitrate radicals with formaldehyde is not expected to be a major loss process under tropospheric conditions.

Overall half-lives for formaldehyde in air can vary considerably under different conditions. Estimations for atmospheric residence time in several US cities ranged from 0.3 h under conditions typical of a rainy winter night to 250 h under conditions typical of a clear summer night (assuming no reaction with hydroperoxyl radicals) (US EPA, 1993). During the daytime, under clear sky conditions, the residence time of formaldehyde is determined primarily by its reaction with the hydroxyl radical. Photolysis accounted for only 2–5% of the removal.

Given the generally short daytime residence times for formaldehyde, there is limited potential for long-range transport of this compound. However, in cases where organic precursors are transported long distances, secondary formation of formaldehyde may occur far from the actual anthropogenic sources of the precursors (Tanner et al., 1994).

Because of its high solubility in water, formaldehyde will transfer into clouds and precipitation. A washout ratio (concentration in rain/concentration in air) of 73 000 at 25 °C is estimated by Atkinson (1990). Gas-phase organic compounds that have a washout ratio of greater than 105 are generally estimated to be efficiently “rained out” (California Air Resources Board, 1993). Based on the washout ratio, the wet deposition (removal of gases and particles by precipitation) of formaldehyde could be significant as a tropospheric loss process (Atkinson, 1989). However, Zafiriou et al. (1980) estimated that rainout was responsible for removing only 1% of formaldehyde produced in the atmosphere by the oxidation of methane. Warneck et al. (1978) showed that washout is important only in polluted regions. Nevertheless, it is expected that wet deposition can lead to a somewhat shorter tropospheric lifetime of formaldehyde than that calculated from gas-phase processes alone.

5.2 Water

In water, formaldehyde is rapidly hydrated to form a glycol. Equilibrium favours the glycol (Dong & Dasgupta, 1986); less than 0.04% by weight of unhydrated formaldehyde is found in highly concentrated solutions (Kroschwitz, 1991). In surface water or groundwater, formaldehyde can be biodegraded (US EPA, 1985; Howard, 1989). Incorporated into atmospheric water, formaldehyde or its hydrate can be oxidized.

Formaldehyde is degraded by various mixed microbial cultures obtained from sludges and sewage (Kitchens et al., 1976; Verschueren, 1983; US EPA, 1985). Formaldehyde in lake water decomposed in approximately 30 h under aerobic conditions at 20 °C and in approximately 48 h under anaerobic conditions (Kamata, 1966). Howard et al. (1991) estimated half-lives of 24–168 h in surface water and 48–336 h in groundwater based on scientific judgement and estimated aqueous aerobic biodegradation half-lives.

When incorporated from air into cloud water, fog water, or rain, formaldehyde can react with aqueous hydroxyl radicals in the presence of oxygen to produce formic acid, water, and hydroperoxide (aqueous). The formaldehyde glycol can also react with ozone (Atkinson et al., 1990).

5.3 Sediment

Because of its low organic carbon/water partition coefficient (K_{oc}) and high water solubility, formaldehyde is not expected to significantly sorb to suspended solids and sediments from water. Biotic and abiotic degradation are expected to be significant processes affecting the fate of formaldehyde in sediment (US EPA, 1985; Howard, 1989).

5.4 Soil

Formaldehyde is not expected to adsorb to soil particles to a great degree and would be considered mobile in the soil, based on its estimated K_{oc} . According to Kenaga (1980), compounds with a K_{oc} of <100 are considered to be moderately mobile. Formaldehyde can be transported to surface water through runoff and to groundwater as a result of leaching. Parameters other than K_{oc} affecting its leaching to groundwater include the soil type, the amount and frequency of rainfall, the depth of the groundwater, and the extent of degradation of formaldehyde. Formaldehyde is susceptible to degradation by various soil microorganisms (US EPA, 1985). Howard et al. (1991) estimated a soil half-life of 24–168 h, based on estimated aqueous aerobic biodegradation half-lives.

5.5 Biota

In view of the very low bioconcentration factor of 0.19, based on a log octanol/water partition coefficient (K_{ow}) of 0.65 (Veith et al., 1980; Hansch & Leo, 1981), formaldehyde is not expected to bioaccumulate. When examined, bioconcentration was not observed in fish or shrimp (Stills & Allen, 1979; Hose & Lightner, 1980).

5.6 Environmental partitioning

Fugacity modelling was carried out to provide an overview of key reaction, intercompartment, and advection (movement out of a system) pathways for formaldehyde and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay & Paterson (1991). Assumptions, input parameters, and results are presented in Mackay et al. (1995) and Environment Canada (1999a).

Based on formaldehyde's physical/chemical properties, Level III fugacity modelling indicates that when formaldehyde is continuously discharged into one medium, most of it can be expected to be present in that medium (Mackay et al., 1995; DMER & AEL, 1996). However, given the uncertainties relating to use of pseudo-solubility, hydration in water, and the complex atmospheric formation and degradation processes for formaldehyde, quantitative estimates of mass distribution are not considered reliable.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data on concentrations in the environment primarily from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as a basis for the sample risk characterization. Patterns of exposure in other countries are expected to be similar, although quantitative values may vary.

6.1 Environmental levels

6.1.1 Ambient air

Formaldehyde was detected (detection limit 0.042 ppb [$0.05 \mu\text{g}/\text{m}^3$]) in 3810 of 3842 24-h samples from rural, suburban, and urban areas, collected at 16 sites in six provinces surveyed from August 1989 to August 1998 (Environment Canada, 1999a). Concentrations ranged from below the detection limit (0.042 ppb [0.05

$\mu\text{g}/\text{m}^3$]) to maxima of 22.9 ppb ($27.5 \mu\text{g}/\text{m}^3$) for eight urban sites, 10.03 ppb ($12.03 \mu\text{g}/\text{m}^3$) for two suburban sites, 7.59 ppb ($9.11 \mu\text{g}/\text{m}^3$) for two rural sites considered to be affected by urban and/or industrial influences, and 8.23 ppb ($9.88 \mu\text{g}/\text{m}^3$) for four rural sites considered to be regionally representative. Long-term (1 month to 1 year) mean concentrations for these sites ranged from 0.65 to 7.30 ppb (0.78 to $8.76 \mu\text{g}/\text{m}^3$). The single highest 24-h concentration measured was 22.9 ppb ($27.5 \mu\text{g}/\text{m}^3$), obtained for an urban sample collected from Toronto, Ontario, on 8 August 1995. Available data indicate that levels are highest between June and August, and there is no evidence that concentrations of formaldehyde were systematically increasing or decreasing at these sites over this 9-year period (Health Canada, 2000).

Atmospheric measurements made in 1992 during the dark winter and sunlit spring of an extremely remote site at Alert, Nunavut, ranged from 0.033 to 0.70 ppb (0.04 to $0.84 \mu\text{g}/\text{m}^3$) on a 5-min basis (detection limit 0.033 ppb [$0.04 \mu\text{g}/\text{m}^3$]), with a mean of 0.40 ppb ($0.48 \mu\text{g}/\text{m}^3$) (De Serves, 1994).

In air near a forest products plant in Canada, the maximum 24-h average concentrations for three 3-month periods between March 1995 and March 1996 ranged from 1.43 to 3.67 ppb (1.71 to $4.40 \mu\text{g}/\text{m}^3$) (detection limit not specified) (Environment Canada, 1997b).

6.1.2 Indoor air

Data concerning concentrations of formaldehyde in residential indoor air from seven studies conducted in Canada between 1989 and 1995 were examined (Health Canada, 2000). Despite differences in sampling mode and duration (i.e., active sampling for 24 h or passive sampling for 7 days), the distributions of concentrations were similar in five of the studies. The median, arithmetic mean, 95th percentile, and 99th percentile concentrations of the pooled data ($n = 151$ samples) from these five studies were 25, 30, 71, and 97 ppb (30, 36, 85, and $116 \mu\text{g}/\text{m}^3$), respectively (Health Canada, 2000). In view of the potential for less dilution from indoor sources in Canadian residential structures owing to lower average air exchange rates due to energy conservation, levels of formaldehyde in indoor air in residences located in warmer climates might be expected to be less. Identified values measured in non-workplace indoor air in other countries are, however, similar to those reported here.

Concurrent 24-h measurements in outdoor air and indoor air of Canadian residences were available from some of these studies. Average concentrations of formaldehyde were an order of magnitude higher in indoor air than in outdoor air, indicating the presence of indoor sources of formaldehyde and confirming similar findings in other countries (IPCS, 1989; ATSDR, 1999).

Information concerning the presence of environmental tobacco smoke (ETS) in the homes sampled was available from some of these studies; however, there was no clear indication that concentrations of formaldehyde were greater in homes where ETS was present. Acetaldehyde, rather than formaldehyde, is the most abundant carbonyl compound in mainstream and sidestream cigarette smoke. Based on data from the USA and elsewhere, ETS does not increase concentrations of formaldehyde in indoor air, except in areas with high rates of smoking and minimal rates of ventilation (Godish, 1989; Guerin et al., 1992).

Data from several studies indicate that various cooking activities may contribute to the elevated levels of formaldehyde sometimes present in indoor air (Health Canada, 2000). In recent work from the USA, the emission rate of formaldehyde from meat charbroiling over a natural gas-fired grill in a commercial facility was higher (i.e., 1.38 g/kg of meat cooked) than emission rates of all other VOCs measured except for ethylene (Schauer et al., 1999).

6.1.3 Water

6.1.3.1 Drinking-water

Representative data concerning concentrations in drinking-water in Canada were not available. The concentration of formaldehyde in drinking-water is likely dependent upon the quality of the raw source water and purification steps (Krasner et al., 1989). Ozonation may slightly increase the levels of formaldehyde in drinking-water, but subsequent purification steps may attenuate these elevated concentrations (Huck et al., 1990). Elevated concentrations have been measured in US houses equipped with polyacetal plumbing elbows and tees. Normally, an interior protective coating prevents water from contacting the polyacetal resin (Owen et al., 1990). However, if routine stress on the supply lines results in a break or fracture of the coating, water may contact the resin directly. The resultant concentrations of formaldehyde in the water are largely determined by the residence time of the water in the pipes. Owen et al. (1990) estimated that at normal water usage rates in occupied dwellings, the resulting concentration of formaldehyde in water would be about 20 µg/litre. In general, concentrations of formaldehyde in drinking-water are expected to be less than 100 µg/litre (IPCS, 1989; IARC, 1995).

6.1.3.2 Surface water

Concentrations of formaldehyde in raw water from the North Saskatchewan River were measured at the Rosedale drinking-water treatment plant in Edmonton, Alberta, Canada. Concentrations between March and

October 1989 averaged 1.2 µg/litre, with a peak value of 9.0 µg/litre. These concentrations were influenced by climatological events such as spring runoff, major rainfall events, and the onset of winter, as evidenced by concentration increases during spring runoff and major rainfall and concentration decreases (<0.2 µg/litre) following river freeze-up (Huck et al., 1990).

Anderson et al. (1995) measured formaldehyde concentrations in the raw water of three drinking-water treatment pilot plants in Ontario, Canada. The study included three distinct types of surface waters, covering a range of characteristics and regional influences: a moderately hard waterway with agricultural impacts (Grand River at Brantford), a soft, coloured river (Ottawa River at Ottawa), and a river with moderate values for most parameters, typical of the Great Lakes waterways (Detroit River at Windsor). Concentrations were less than the detection limit (1.0 µg/litre) and 8.4 µg/litre in raw water samples collected on 2 December 1993 and 15 February 1994, respectively, from the Detroit River. In the Ottawa River, concentrations were below the detection limit (1.0 µg/litre) in three profiles taken between 12 April and 7 June 1994. In the Grand River, a mean concentration of 1.1 µg/litre was obtained for seven sampling dates between 11 May and 21 June 1994.

6.1.3.3 Effluent

The highest reported concentration from one of the four plants reporting releases for 1997 (Environment Canada, 1999b) was a 1-day mean of 325 µg/litre, with a 4-day mean of 240 µg/litre (Environment Canada, 1999a).

6.1.3.4 Groundwater

Extensive monitoring of groundwater from a Canadian site of production and use of formaldehyde included 10 samples in which formaldehyde concentrations were below the detection limit (50 µg/litre) and 43 samples with concentrations ranging from 65 to 690 000 µg/litre (mean of two duplicates) from November 1991 to February 1992 (Environment Canada, 1997b). Data had been collected as part of a monitoring programme to delineate the boundaries of groundwater contamination at the facility and were used to design a groundwater containment and recovery system. Formaldehyde was not detected in samples taken from outside the contaminated zone.

Quarterly analyses of five monitoring wells on the property of a Canadian plant that produces UF resins were carried out during 1996–1997. Concentrations ranged from below the detection limit (50 µg/litre) to 8200 µg/litre, with an overall median of 100 µg/litre. Concentrations for different wells indicated little disper-

sion from wells close to the source of contamination (Environment Canada, 1997b).

Groundwater samples collected from wells downstream from six cemeteries in Ontario, Canada, contained concentrations of formaldehyde of 1–30 µg/litre (detection limit not specified), although a blank sample contained 7.3 µg/litre in these analyses (Chan et al., 1992).

6.1.3.5 Atmospheric water

Concentrations of formaldehyde in rain ranged from 0.44 µg/litre (near Mexico City) to 3003 µg/litre (during the vegetation burning season in Venezuela; anthropogenic sources). Mean concentrations ranged from 77 µg/litre (in Germany) to 321 µg/litre (during the non-burning season in Venezuela). In snow, concentrations of formaldehyde ranged from 18 to 901 µg/litre in California, USA. A mean snow concentration of 4.9 µg/litre is reported for Germany. In fog water, concentrations of 480–17 027 µg/litre have been measured in the Po valley, Italy, with a mean of 3904 µg/litre (Environment Canada, 1999a).

6.1.4 Sediment and soil

No data were identified on concentrations of formaldehyde in sediments in the source country (Canada).

Concentrations in soil were measured at manufacturing plants that use phenol/formaldehyde resins. At a plywood plant, six soil samples collected in 1991 contained formaldehyde concentrations of 73–80 mg/kg, with a mean of 76 mg/kg (detection limit not specified) (G. Dinwoodie, personal communication, 1996). At a fibreglass insulation plant, formaldehyde was not detected (detection limit 0.1 mg/kg) in soil samples collected in 1996 from six depths at four industrial areas on-site. Formaldehyde was also not detected in samples taken from a non-industrial site 120 km away from the plant.

6.1.5 Biota

No data were identified on concentrations of formaldehyde in biota in the source country (Canada).

6.1.6 Food

There have been no systematic investigations of levels of formaldehyde in a range of foodstuffs as a basis for estimation of population exposure (Health Canada, 2000). Although formaldehyde is a natural component of a variety of foodstuffs (IPCS, 1989; IARC, 1995), monitoring has generally been sporadic and source directed. Available data suggest that the highest

concentrations of formaldehyde naturally occurring in foods (i.e., up to 60 mg/kg) are in some fruits (Möhler & Denbsky, 1970; Tsuchiya et al., 1975) and marine fish (Rehbein, 1986; Tsuda et al., 1988).

Formaldehyde develops postmortem in marine fish and crustaceans, from the enzymatic reduction of trimethylamine oxide to formaldehyde and dimethylamine (Sotelo et al., 1995). While formaldehyde may be formed during the ageing and deterioration of fish flesh, high levels do not accumulate in the fish tissues, due to subsequent conversion of the formaldehyde formed to other chemical compounds (Tsuda et al., 1988). However, formaldehyde accumulates during the frozen storage of some fish species, including cod, pollack, and haddock (Sotelo et al., 1995). Formaldehyde formed in fish reacts with protein and subsequently causes muscle toughness (Yasuhara & Shibamoto, 1995), which suggests that fish containing the highest levels of formaldehyde (e.g., 10–20 mg/kg) may not be considered palatable as a human food source.

Higher concentrations of formaldehyde (i.e., up to 800 mg/kg) have been reported in fruit and vegetable juices in Bulgaria (Tashkov, 1996); however, it is not clear if these elevated levels arise during processing. Formaldehyde is used in the sugar industry to inhibit bacterial growth during juice production (ATSDR, 1999). In a study conducted by Agriculture Canada, concentrations of formaldehyde were higher in sap from maple trees that had been implanted with paraformaldehyde to deter bacterial growth in tap holes (Baraniak et al., 1988). The resulting maple syrup contained concentrations up to 14 mg/kg, compared with less than 1 mg/kg in syrup from untreated trees.

In other processed foods, the highest concentrations (i.e., 267 mg/kg) have been reported in the outer layer of smoked ham (Brunn & Klostermeyer, 1984) and in some varieties of Italian cheese, where formaldehyde is permitted for use under regulation as a bacteriostatic agent (Restani et al., 1992). Hexamethylenetetramine, a complex of formaldehyde and ammonia that decomposes slowly to its constituents under acid conditions, has been used as a food additive in fish products such as herring and caviar in the Scandinavian countries (Scheuplein, 1985).

Concentrations of formaldehyde in a variety of alcoholic beverages ranged from 0.04 to 1.7 mg/litre in Japan (Tsuchiya et al., 1994) and from 0.02 to 3.8 mg/litre in Brazil (de Andrade et al., 1996). In earlier work conducted in Canada, Lawrence & Iyengar (1983) compared levels of formaldehyde in bottled and canned cola soft drinks (7.4–8.7 mg/kg) and beer (0.1–1.5 mg/kg) and concluded that there was no significant increase in the formaldehyde content of canned beverages due to the

plastic inner coating of the metal containers. Concentrations of 3.4 and 4.5 mg/kg in brewed coffee and 10 and 16 mg/kg in instant coffee were reported in the USA (Hayashi et al., 1986). These concentrations reflect the levels in the beverages as consumed.

Formaldehyde is used in the animal feed industry, where it is added to ruminant feeds to improve handling characteristics. The food mixture contains less than 1% formaldehyde, and animals may ingest as much as 0.25% formaldehyde in their diet (Scheuplein, 1985). Formalin has been added as a preservative to skim milk fed to pigs in the United Kingdom (Florence & Milner, 1981) and to liquid whey (from the manufacture of cheddar and cottage cheeses) fed to calves and cows in Canada. Maximum concentrations in the milk of cows fed whey with the maximum level of formalin tested (i.e., 0.15%) were up to 10-fold greater (i.e., 0.22 mg/kg) than levels in milk from control cows fed whey without added formalin (Buckley et al., 1986, 1988). In a more recent study, the concentrations of formaldehyde in commercial 2% milk and in fresh milk from cows fed on a typical North American dairy total mixed diet were determined. Concentrations in the fresh milk (i.e., from Holstein cows, morning milking) ranged from 0.013 to 0.057 mg/kg, with a mean concentration ($n = 18$) of 0.027 mg/kg, while concentrations in processed milk (i.e., 2% milk fat, partly skimmed, pasteurized) ranged from 0.075 to 0.255 mg/kg, with a mean concentration ($n = 12$) of 0.164 mg/kg. The somewhat higher concentrations in the commercial 2% milk were attributed to processing technique, packaging, and storage, but these factors were not assessed further (Kaminski et al., 1993).

The degree to which formaldehyde in various foods is bioavailable following ingestion is not known.

6.1.7 Consumer products

Formaldehyde and formaldehyde derivatives are present in a wide variety of consumer products (Preuss et al., 1985) to protect the products from spoilage by microbial contamination. Formaldehyde is used as a preservative in household cleaning agents, dishwashing liquids, fabric softeners, shoe care agents, car shampoos and waxes, carpet cleaning agents, etc. (IPCS, 1989). Levels of formaldehyde in hand dishwashing liquids and liquid personal cleansing products available in Canada are less than 0.1% (w/w) (A. McDonald, personal communication, 1996).

Formaldehyde has been used in the cosmetics industry in three principal areas: preservation of cosmetic products and raw materials against microbial contamination, certain cosmetic treatments such as hardening of fingernails, and plant and equipment sanitation (Jass, 1985). Formaldehyde is also used as an

antimicrobial agent in hair preparations, lotions (e.g., suntan lotion and dry skin lotion), makeup, and mouthwashes and is also present in hand cream, bath products, mascara and eye makeup, cuticle softeners, nail creams, vaginal deodorants, and shaving cream (IPCS, 1989; ATSDR, 1999).

Some preservatives are formaldehyde releasers. The release of formaldehyde upon their decomposition is dependent mainly on temperature and pH. Information on product categories and typical concentrations for chemical products containing formaldehyde and formaldehyde releasers was obtained from the Danish Product Register Data Base (PROBAS) by Flyvholm & Andersen (1993). Industrial and household cleaning agents, soaps, shampoos, paints/lacquers, and cutting fluids comprised the most frequent product categories for formaldehyde releasers. The three most frequently registered formaldehyde releasers were bromonitropropanediol, bromonitrodioxane, and chloroallylhexaminium chloride (Flyvholm & Andersen, 1993).

Formaldehyde is present in the smoke resulting from the combustion of tobacco products. Estimates of emission factors for formaldehyde (e.g., $\mu\text{g}/\text{cigarette}$) from mainstream and sidestream smoke and from ETS have been determined by a number of different protocols for cigarettes in several countries.

A range of mainstream smoke emission factors from 73.8 to 283.8 $\mu\text{g}/\text{cigarette}$ was reported for 26 US brands, which included non-filter, filter, and menthol cigarettes of various lengths (Miyake & Shibamoto, 1995). Differences in concentrations reflect differences in tobacco type and brand. More recent information is available from the British Columbia Ministry of Health from tests conducted on 11 brands of Canadian cigarettes. Mainstream smoke emission factors ranged from 8 to 50 $\mu\text{g}/\text{cigarette}$ when tested under standard conditions.¹

Levels of formaldehyde are higher in sidestream smoke than in mainstream smoke. Guerin et al. (1992) reported that popular commercial US cigarettes deliver approximately 1000–2000 μg formaldehyde/cigarette in their sidestream smoke. Schlitt & Knöppel (1989) reported a mean ($n = 5$) formaldehyde content of 2360 $\mu\text{g}/\text{cigarette}$ in the sidestream smoke from a single brand in Italy. Information from the British Columbia Ministry of Health from tests conducted on 11 brands of

¹ Data from British Columbia Ministry of Health web site (www.cctc.ca/bcreorts/results.htm) regarding emission factors of toxic chemicals from mainstream and sidestream smoke from 11 brands of Canadian cigarettes. Victoria, British Columbia, 1998.

Canadian cigarettes indicates that emission factors from sidestream smoke ranged from 368 to 448 $\mu\text{g}/\text{cigarette}$.¹

Emission factors for toxic chemicals from ETS, rather than from mainstream or sidestream smoke, have also been determined. This is in part due to concerns that emission factors for sidestream smoke may be too low for reactive chemicals such as formaldehyde, due to losses in the various apparatus used to determine sidestream smoke emission factors. Daisey et al. (1994) indicated that ETS emission factors for formaldehyde from six US commercial cigarettes ranged from 958 to 1880 $\mu\text{g}/\text{cigarette}$, with a mean of $1310 \pm 349 \mu\text{g}/\text{cigarette}$. Data concerning emission factors for formaldehyde from ETS produced by Canadian cigarettes were not identified.

6.1.7.1 Clothing and fabrics

Formaldehyde-releasing agents provide crease resistance, dimensional stability, and flame retardance for textiles and serve as binders in textile printing (Priha, 1995). Durable-press resins or permanent-press resins containing formaldehyde have been used on cotton and cotton/polyester blend fabrics since the mid-1920s to impart wrinkle resistance during wear and laundering. Hatch & Maibach (1995) identified nine major resins used. These differ in formaldehyde-releasing potential during wear and use.

Priha (1995) indicated that formaldehyde-based resins, such as UF resin, were once more commonly used for crease resistance treatment; more recently, however, better finishing agents with lower formaldehyde release have been developed. Totally formaldehyde-free cross-linking agents are now available, and some countries have legally limited the formaldehyde content of textile products. In 1990, the percentage of durable-press fabric manufactured in the USA finished with resins rated as having high formaldehyde release was 27%, about one-half the percentage in 1980, according to Hatch & Maibach (1995). It has been reported that the average level contained by textiles made in the USA is approximately 100–200 μg free formaldehyde/g (Scheman et al., 1998).

Piletta-Zanin et al. (1996) studied the presence of formaldehyde in moist baby toilet tissues and tested 10 of the most frequently sold products in Switzerland. One product contained more than 100 $\mu\text{g}/\text{g}$, five products contained between 30 and 100 $\mu\text{g}/\text{g}$, and the remaining four products contained less than 30 μg formaldehyde/g.

6.1.7.2 Building materials

The emission of formaldehyde from building materials has long been recognized as a significant source of the elevated concentrations of formaldehyde

frequently measured in indoor air. Historically, the most important indoor source among the many materials used in building and construction has been urea-formaldehyde foam insulation (UFFI), which is produced by the aeration of a mixture of UF resin and an aqueous surfactant solution containing a curing catalyst (Meek et al., 1985). UFFI was banned from use in Canada in 1980 and in the USA in 1982, although the US ban was subsequently overturned.

Pressed wood products (i.e., particleboard, medium-density fibreboard, and hardwood plywood) are now considered the major sources of residential formaldehyde contamination (Godish, 1988; Etkin, 1996). Pressed wood products are bonded with UF resin; it is this adhesive portion that is responsible for the emission of formaldehyde into indoor air. The emission rate of formaldehyde is strongly influenced by the nature of the material. Generally, release of formaldehyde is highest from newly made wood products. Emissions then decrease over time, to very low rates, after a period of years (Godish, 1988).

Concentrations of formaldehyde in indoor air are primarily determined by such factors as source strength (i.e., mass of substance released per unit time or per unit area), loading factors (i.e., the ratio of the surface area of a source [e.g., a particleboard panel] to the volume of an enclosed area [e.g., a room] where the source is present), and the presence of source combinations (Godish, 1988). Emission rates for formaldehyde from pressed wood products determined by emission chamber testing in Canada (Figley & Makohon, 1993; Piersol, 1995), the United Kingdom (Crump et al., 1996), and the USA (Kelly et al., 1999) are now typically less than 0.3 mg/m^2 per hour (Health Canada, 2000).

Formaldehyde release from pressed wood materials is greater in mobile homes than in conventional housing, as mobile homes typically have higher loading ratios (e.g., exceeding 1 m^2/m^3) of these materials. In addition, mobile homes can have minimal ventilation, are minimally insulated, and are often situated in exposed sites subject to temperature extremes (Meyer & Hermanns, 1985).

The use of scavengers (e.g., urea) to chemically remove unreacted formaldehyde while the curing process is taking place has been investigated as a control measure. Other reactants could be used to chemically modify the formaldehyde to a non-toxic derivative or convert it to a non-volatile reaction product. There has also been work to effectively seal the resin and prevent the residual formaldehyde from escaping (Tabor, 1988). Surface coatings and treatments (e.g., paper and vinyl decorative laminates) can significantly affect the potential for off-gassing and in some cases can result in an order of magnitude reduction

in the emission rates for formaldehyde from pressed wood products (Figley & Makohon, 1993; Kelly et al., 1999). On the other hand, high emissions of formaldehyde during the curing of some commercially available conversion varnishes (also known as acid-catalyst varnishes) have been reported. An initial emission rate of 29 mg formaldehyde/m² per hour was determined for one product (McCrillis et al., 1999).

Emission rates for formaldehyde from carpets and carpet backings, vinyl floorings, and wall coverings in the source country (Canada) are now generally less than 0.1 mg/m² per hour (Health Canada, 2000).

6.2 Human exposure: environmental

This sample exposure estimation is based primarily on data on concentrations in the environment from the source country of the national assessment on which the CICAD is based (i.e., Canada) as a basis for the sample risk characterization. Owing to the ubiquitous sources of formaldehyde, which are likely similar in most countries, the overall magnitude of relative contributions from various sources of exposure presented here are expected to be reasonably representative of those in other parts of the world.

Estimates of the total daily intake of formaldehyde by six age groups of the general population of Canada were developed primarily to determine the relative contributions from various media. These estimates indicate that the daily intake of formaldehyde via inhalation is consistently less than that estimated for the ingestion of foodstuffs. However, it should be noted that critical effects associated with exposure to formaldehyde occur primarily at the site of first contact (i.e., the respiratory tract following inhalation and the aerodigestive tract, including oral and gastrointestinal mucosa, following ingestion) and are related to the concentration of formaldehyde in media to which humans are exposed, rather than to the total intake of this substance. For this reason, effects of exposure by inhalation and ingestion are addressed separately.

Due primarily to limitations of available data as a basis for characterization of exposure via ingestion, the principal focus of the assessment is airborne exposure. The less representative assessment for ingestion involves comparison of the concentration of formaldehyde in a limited number of food products with a tolerable concentration (ingestion).

A subset of data from the National Air Pollution Surveillance programme was selected to represent the range and distribution of concentrations to which the general population of Canada is currently assumed to be exposed via inhalation of outdoor air (Table 4).

Pooled data ($n = 151$) from five studies in which concentrations of formaldehyde were measured in the indoor air of residences in Canada between 1989 and 1995 were the basis for the range and distribution of concentrations to which the general population of Canada is currently assumed to be exposed via inhalation of residential indoor air (Health Canada, 2000) (Table 4).

The distribution of the time spent outdoors is arbitrarily assumed to be normal in shape with an arithmetic standard deviation of 2 h. In the probabilistic simulation, this distribution is truncated at 0 h and 9 h. The time spent indoors is calculated as 24 h minus the time spent outdoors. Individuals residing in warmer climates may spend a greater amount of time outdoors.

Estimates of the distribution of time-weighted 24-h concentrations of formaldehyde to which the general population is exposed were developed using simple random sampling (Monte Carlo analysis) with Crystal Ball™ Version 4.0 (Decisioneering, Inc., 1996) and simulations of 10 000 trials.

Two simulations were run. The parameters for the simulations and estimates of the median, arithmetic mean, and upper percentiles of the distributions of 24-h time-weighted average concentrations of formaldehyde determined from these probabilistic simulations are summarized in Table 5. Based on the assumptions underlying these probabilistic simulations, the estimates summarized in Table 5 indicate that one of every two persons would be exposed to 24-h average concentrations of formaldehyde in air of 20–24 ppb (24–29 µg/m³) or greater (i.e., median concentrations). Similarly, 1 in 20 persons (i.e., 95th percentile) would be exposed to 24-h average concentrations of formaldehyde in air of 67–78 ppb (80–94 µg/m³) or greater.

Based on limited data from the USA, concentrations in drinking-water may range up to approximately 10 µg/litre, in the absence of specific contributions from the formation of formaldehyde by ozonation during water treatment or from leaching of formaldehyde from polyacetal plumbing fixtures. One-half this concentration (i.e., 5 µg/litre) was judged to be a reasonable estimate of the average concentration of formaldehyde in Canadian drinking-water, in the absence of other data. Concentrations approaching 100 µg/litre were observed in a US study assessing the leaching of formaldehyde from domestic polyacetal plumbing fixtures, and this concentration is assumed to be representative of a reasonable worst case.

Similarly, very few data are available with which to estimate the range and distribution of concentrations of formaldehyde in foods to which the general population

in Canada is exposed. According to the limited available data, concentrations of formaldehyde in food are highly variable. In the few studies of the formaldehyde content of foods in Canada, the concentrations of formaldehyde were within the range <0.03–14 mg/kg (Health Canada, 2000). However, the proportion of formaldehyde in foods that is bioavailable is unknown. Formaldehyde is a metabolite of methanol (IPCS, 1997).

6.3 Human exposure: occupational

Since the principal focus of the source document was on exposure in the general environment, the following provides only a brief overview of occupational exposure to formaldehyde. Occupational exposure to formaldehyde occurs in all workplaces, as the sources (e.g., combustion) are ubiquitous. Although it is not possible to accurately estimate the number of people

Table 4: Concentrations of formaldehyde in outdoor air and residential indoor air in Canada.

Medium of exposure	Number of samples	Mid-points of distributions ($\mu\text{g}/\text{m}^3$)		Upper percentiles of distributions of concentrations ($\mu\text{g}/\text{m}^3$)			
		Median	Mean ^a	75th	90th	95th	97.5th
Outdoor air – NAPS data ^b	2819	2.8	3.3	4.1	6.0	7.3	9.1
Outdoor air – reasonable worst-case site ^c	371	2.9	4.0	4.8	7.3	10.4	17.3
Indoor air – five studies ^d	151	29.8	35.9	46.2	64.8	84.6	104.8
Indoor air – lognormal distribution ^e	–	28.7	–	46.1	70.7	91.2	113.8

- ^a These are the arithmetic mean concentrations. Since formaldehyde was detected in more than 99% of the samples, censoring of the data for limit of detection was not required.
- ^b Data are for selected suburban ($n = 4$) and urban ($n = 4$) sites of the National Air Pollution Surveillance (NAPS) programme (T. Dann, unpublished data, 1997, 1999) for the period 1990–1998. Concentrations are slightly lower for the subset of suburban sites and slightly higher for the subset of urban sites. Distributions are positively skewed.
- ^c One of the four urban sites (i.e., NAPS site 060418 in Toronto) was selected for the reasonable worst-case purpose.
- ^d Data were pooled from five studies of concentrations of formaldehyde in residential indoor air. These studies were conducted at various locations in Canada between 1989 and 1995.
- ^e The geometric mean and standard deviation of the pooled data ($n = 151$) from the five Canadian studies were calculated. A lognormal distribution with the same geometric mean and standard deviation was generated, and the upper percentiles of this distribution were estimated.

Table 5: Probabilistic estimates of 24-h time-weighted average concentrations of formaldehyde in air.

	Mid-points of distributions ($\mu\text{g}/\text{m}^3$)		Upper percentiles of distributions of concentrations ($\mu\text{g}/\text{m}^3$) and relative standard deviations (%)			
	Median	Mean ^a	75th	90th	95th	97.5th
Simulation 1 ^b	29	36	46 ($\pm 0.5\%$)	62 ($\pm 1.3\%$)	80 ($\pm 1.9\%$)	97 ($\pm 0.7\%$)
Simulation 2 ^c	24	33	45 ($\pm 1.2\%$)	75 ($\pm 1.2\%$)	94 ($\pm 1.6\%$)	109 ($\pm 1.3\%$)

- ^a This is the arithmetic mean concentration.
- ^b In simulation 1, the distribution of concentrations of formaldehyde is represented by a frequency histogram of the pooled data from the five selected studies ($n = 151$ samples).
- ^c For simulation 2, a lognormal distribution of concentrations, truncated at $150 \mu\text{g}/\text{m}^3$, is assumed. This lognormal distribution has the same geometric mean ($28.7 \mu\text{g}/\text{m}^3$) and standard deviation (2.92) as the distribution of concentrations for the pooled data from the five selected studies.

occupationally exposed to formaldehyde worldwide, it is likely to be several millions in industrialized countries alone (IARC, 1995). Industries with greatest potential exposure include health services, business services, printing and publishing, manufacture of chemicals and allied products, apparel and allied products, paper and allied products, personal services, machinery except

clerical, transport equipment, and furniture and fixtures (IARC, 1995).

Formaldehyde occurs in occupational environments mainly as a gas. Formaldehyde-containing particles can also be inhaled when paraformaldehyde or powdered resins are being used in the workplace (IARC, 1995). These resins can also be attached to carriers, such

as wood dust. Exposure may also occur dermally when formalin solutions or liquid resins come into contact with skin.

Exposure concentrations are highly variable between workplaces. The reported mean concentrations in the air of factories producing formaldehyde-based resins vary from <1 to >10 ppm (<1.2 to >12 mg/m³) (IARC, 1995). Formaldehyde-based glues have been used in the assembly of plywood and particleboard for over 30 years, and concentrations in these factories were usually >1 ppm (>1.2 mg/m³) before the mid-1970s but have been below that level more recently (IARC, 1995). The development of glues with lower formaldehyde content and better ventilation has reduced concentrations to about 1 ppm (1.2 mg/m³) or below (Kauppinen & Niemelä, 1985). Furniture varnishes may contain UF resins dissolved in organic solvents. As a result, workers are continuously exposed to an average level of about 1 ppm (1.2 mg/m³), but the levels have decreased slightly since 1975 (Priha et al., 1986). Coating agents and other chemicals used in paper mills may contain formaldehyde as a bactericide. The average levels related to lamination and impregnation of paper in mills in the USA, Sweden, and Finland were usually below 1 ppm (1.2 mg/m³), but variation can occur depending on the type of resin used and the product manufactured (IARC, 1995).

Formaldehyde has been used in the textile industry to produce crease-resistant and flame-retardant fabrics. These fabrics release formaldehyde into the air of the plants, leading to average concentrations of 0.2–2 ppm (0.24–2.4 mg/m³) in the late 1970s and 1980s. Measurements from the 1980s indicate that levels are dropping owing to the lower content of formaldehydes in fabrics (IARC, 1995).

Formaldehyde-based resins are commonly used as core binders in foundries. The mean levels of formaldehyde in core-making and post-core-making operations in the 1980s in Sweden and Finland were usually below 1 ppm (1.2 mg/m³). Formaldehyde-based plastics are used in the production of electrical parts, dishware, and various other products. The concentrations measured in such industries have usually been below 1 ppm (1.2 mg/m³), but much higher concentrations may occur, especially in factories creating moulded plastic products (IARC, 1995). The heating of bake-drying paints and soldering as well as the coating and development of photographic films can lead to the release of small amounts of formaldehyde in the workplace, but levels are usually well below 1 ppm (1.2 mg/m³) (IARC, 1995). Formaldehyde can also be released or formed during the preservation of fur, leather, barley, and sugar beets and during many other industrial operations. Some of these

activities can result in heavy exposures, with high peak exposure occurring many times per day.

Formaldehyde is used as a tissue preservative and disinfectant in embalming fluids. The concentration of formaldehyde in the air during embalming is variable, but the mean level is about 1 ppm (1.2 mg/m³) (IARC, 1995). The mean concentrations of formaldehyde measured in hospitals range from 0.083 to 0.83 ppm (0.1 to 1.0 mg/m³), but the measurements were made during disinfection, which usually takes a relatively short time. Formalin solution is commonly used to preserve tissue samples in histopathology laboratories. The concentrations are sometimes high, but the mean level during exposure is about 0.5 ppm (0.6 mg/m³) (IARC, 1995).

Occupational exposure to formaldehyde may also occur in the construction industry, agriculture, forestry, and the service sector. Specialized workers can be exposed to very high concentrations. For example, workers who varnish wood floors are exposed to mean levels of 2–5 ppm (2.4–6.0 mg/m³) during each coat. Each worker may complete 5–10 coats of varnish per day (IARC, 1995). Formaldehyde is used in agriculture as a preservative for fodder and as a disinfectant for brooding houses. Although exposure is high at the time of application (7–8 ppm [8.4–9.6 mg/m³]), the annual exposure from this source remains very low (Heikkilä et al., 1991). Lumberjacks can also be exposed to formaldehyde from the exhaust of their chainsaws; however, the average exposure in Sweden and Finland was <0.1 ppm (<0.12 mg/m³) (IARC, 1995).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Formaldehyde is formed endogenously during the metabolism of amino acids and xenobiotics. *In vivo*, most formaldehyde is probably bound (reversibly) to macromolecules.

Owing to its reactivity with biological macromolecules, most of the formaldehyde that is inhaled is deposited and absorbed in regions of the upper respiratory tract with which the substance comes into first contact (Heck et al., 1983; Swenberg et al., 1983; Patterson et al., 1986). In rodents, which are obligate nose breathers, deposition and local absorption occur primarily in the nasal passages; in oronasal breathers (such as monkeys and humans), they likely occur primarily in the nasal passages and oral mucosa, but also in the trachea and bronchus. Species-specific differences in the actual sites

of uptake of formaldehyde and associated lesions of the upper respiratory tract are determined by complex interactions among nasal anatomy, ventilation, and breathing patterns (e.g., nasal versus oronasal) (Monticello et al., 1991).

Formaldehyde produces intra- and intermolecular crosslinks within proteins and nucleic acids upon absorption at the site of contact (Swenberg et al., 1983). It is also rapidly metabolized to formate by a number of widely distributed cellular enzymes, the most important of which is NAD⁺-dependent formaldehyde dehydrogenase. Metabolism by formaldehyde dehydrogenase occurs subsequent to formation of a formaldehyde-glutathione conjugate. Formaldehyde dehydrogenase has been detected in human liver and red blood cells and in a number of tissues (e.g., respiratory and olfactory epithelium, kidney, and brain) in the rat.

Due to its deposition principally within the respiratory tract and rapid metabolism, exposure to concentrations of formaldehyde of 1.9 ppm (2.3 mg/m³), 14.4 ppm (17.3 mg/m³), or 6 ppm (7.2 mg/m³) has not been shown to result in an increase in concentrations of formaldehyde in blood in humans, rats, and monkeys, respectively (Heck et al., 1985; Casanova et al., 1988).

In animal species, the half-life of formaldehyde (administered intravenously) in the circulation ranges from approximately 1 to 1.5 min (Rietbrock, 1969; McMartin et al., 1979). Formaldehyde and formate are incorporated into the one-carbon pathways involved in the biosynthesis of proteins and nucleic acids. Owing to the rapid metabolism of formaldehyde, much of this material is eliminated in the expired air (as carbon dioxide) shortly after exposure. Excretion of formate in the urine is the other major route of elimination of formaldehyde (Johansson & Tjälve, 1978; Heck et al., 1983; Billings et al., 1984; Keefer et al., 1987; Upreti et al., 1987; Bhatt et al., 1988).

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

Information on non-neoplastic effects associated with the repeated inhalation or oral exposure of laboratory animals to formaldehyde is summarized in Tables 6 and 7, respectively.

8.1 Single exposure

Reported LC₅₀s in rodents for the inhalation of formaldehyde range from 414 ppm (497 mg/m³) (in mice exposed for 4 h) to 820 ppm (984 mg/m³) (in rats exposed

for 30 min) (IPCS, 1989). For rats and guinea-pigs, oral LD₅₀s of 800 and 260 mg/kg body weight have been reported (IPCS, 1989). Acute exposure of animals to elevated concentrations of inhaled formaldehyde (e.g., >100 ppm [$>120 \text{ mg/m}^3$]) produces dyspnoea, vomiting, hypersalivation, muscle spasms, and death (IPCS, 1989). Alterations in mucociliary clearance and histopathological changes within the nasal cavity have been observed in rats exposed acutely to formaldehyde at concentrations of 2.2 ppm (2.6 mg/m³) (Monteiro-Riviere & Popp, 1986; Morgan et al., 1986a; Bhalla et al., 1991).

8.2 Short- and medium-term exposure

8.2.1 Inhalation

Histopathological effects and an increase in cell proliferation have been observed in the nasal and respiratory tracts of laboratory animals repeatedly exposed by inhalation to formaldehyde for up to 13 weeks. Most short- and medium-term inhalation toxicity studies have been conducted in rats, with histopathological effects (e.g., hyperplasia, squamous metaplasia, inflammation, erosion, ulceration, disarrangements) and sustained proliferative response in the nasal cavity at concentrations of 3.1 ppm (3.7 mg/m³) and above. Effects were generally not observed at 1 or 2 ppm (1.2 or 2.4 mg/m³), although there have been occasional reports of small, transient increases in epithelial cell proliferation at lower concentrations (Swenberg et al., 1983; Zwart et al., 1988). Owing to the reactivity of this substance as well as to differences in breathing patterns between rodents and primates, adverse effects following short-term inhalation exposure of formaldehyde in rodents are generally restricted to the nasal cavity, while effects in primates may be observed deeper within the respiratory tract. The development of histopathological changes and/or increases in epithelial cell proliferation within the nasal cavity of rats appear to be more closely related to the concentration of formaldehyde to which the animals are exposed than to the total dose (i.e., cumulative exposure) (Swenberg et al., 1983, 1986; Wilmer et al., 1987, 1989).

8.2.2 Oral exposure

Data on toxicological effects arising from short-term oral exposure are limited to one study in which histopathological effects in the forestomach were not observed in Wistar rats receiving 25 mg/kg body weight per day in drinking-water over a period of 4 weeks (Til et al., 1988). Information on toxicological effects of the medium-term oral exposure of laboratory animals to formaldehyde is limited to single studies in rats and dogs, in which the target intakes may not have been achieved (Johansen et al., 1986). Reduction of weight gain in both species was observed at 100 mg/kg body

Table 6: Summary of non-neoplastic effect levels (inhalation) for formaldehyde in animals.

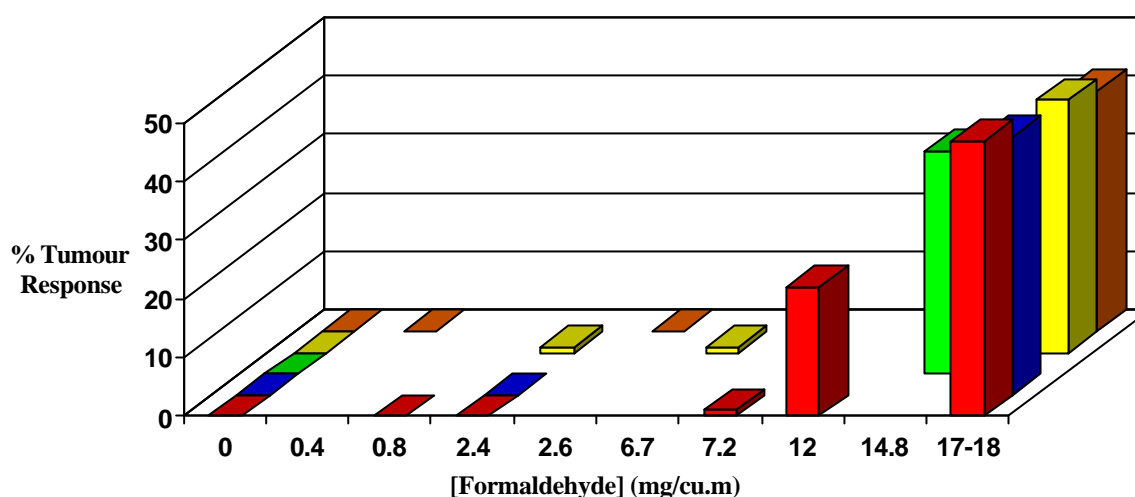
Protocol	Effect levels (mg/m ³)		Critical effect [comments]	Reference
	NO(A)EL	LO(A)EL		
Short-term toxicity				
F344 rats and B6C3F ₁ mice exposed to 0, 0.5, 2, 6, or 15 ppm (0, 0.6, 2.4, 7.2, or 18 mg/m ³) formaldehyde for 6 h/day for 3 days.	2.4 (rats) 7.2 (mice)	7.2 (rats) 18 (mice)	Increased cell proliferation in nasal cavity. In rats, a small transient increase in cell proliferation was observed following exposure to 0.6 mg/m ³ (and to a lesser extent to 2.4 mg/m ³) after 1 day of exposure only. [number and sex of animals not specified]	Swenberg et al., 1983, 1986
Groups of six male F344 rats exposed to 0, 0.5, 2, 5.9, or 14.4 ppm (0, 0.6, 2.4, 7.1, or 17.3 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 1, 2, 4, 9, or 14 days.	2.4	7.1	Histopathological effects in nasal cavity. Inhibition of mucociliary clearance.	Morgan et al., 1986b
Groups of 10 male Wistar rats exposed to 0, 5, or 10 ppm (0, 6, or 12 mg/m ³) formaldehyde for 8 h/day ("continuous exposure") or to 10 or 20 ppm (12 or 24 mg/m ³) formaldehyde for eight 30-min exposure periods separated by 30-min intervals ("intermittent exposure"), 5 days/week for 4 weeks.		6	Histopathological effects and increased cell proliferation in nasal cavity. In animals with the same daily cumulative exposure to formaldehyde, the effects were greater in animals exposed intermittently to the higher concentration.	Wilmer et al., 1987
Groups of three male rhesus monkeys exposed to 0 or 6 ppm (0 or 7.2 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for either 1 or 6 weeks.		7.2	Histopathological effects and increased cell proliferation in nasal cavity and upper portions of respiratory tract. [exposure to formaldehyde had no histopathological effect on the lungs or other internal organs]	Monticello et al., 1989
Groups of 10 male Wistar rats exposed to 0, 0.3, 1.1, or 3.1 ppm (0, 0.36, 1.3, or 3.7 mg/m ³) formaldehyde for 22 h/day for 3 consecutive days.	1.3	3.7	Histopathological effects and increased cell proliferation in nasal cavity.	Reuzel et al., 1990
Groups of 36 male F344 rats exposed to 0, 0.7, 2, 6.2, 9.9, or 14.8 ppm (0, 0.84, 2.4, 7.4, 11.9, or 17.8 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 1, 4, or 9 days or 6 weeks.	2.4	7.4	Histopathological effects and increased cell proliferation in nasal cavity. [exposure to formaldehyde had no histopathological effect on the lungs, trachea, or carina]	Monticello et al., 1991
Groups of 5–6 Wistar rats exposed to 0, 1, 3.2, or 6.4 ppm (0, 1.2, 3.8 or 7.7 mg/m ³) formaldehyde, 6 h/day for 3 consecutive days.	1.2	3.8	Histopathological effects and increased cell proliferation in nasal cavity.	Cassee et al., 1996
Subchronic toxicity				
Groups of 10 male and female Wistar rats exposed to 0, 1, 9.7, or 19.8 ppm (0, 1.2, 11.6, or 23.8 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 13 weeks.	1.2	11.6	Histopathological effects in nasal cavity. [exposure of males to 23.8 mg/m ³ produced non-significant increase in incidence of histopathological effects in the larynx. The authors noted minimal focal squamous metaplasia within the respiratory epithelium in a small number (2/10 males, 1/10 females) of animals exposed to 1.2 mg/m ³]	Woutersen et al., 1987
Groups of 10 male Wistar rats exposed to 0, 0.1, 1.0, or 9.4 ppm (0, 0.12, 1.2, or 11.3 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 13 weeks.	1.2	11.3	Histopathological effects in nasal cavity. [exposure to formaldehyde had no effect upon hepatic protein or glutathione levels]	Appelman et al., 1988
Groups of 50 male and female Wistar rats exposed to 0, 0.3, 1, or 3 ppm (0, 0.36, 1.2, or 3.6 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 13 weeks.	1.2	3.6	Histopathological effects and increased cell proliferation in nasal cavity. [mostly qualitative description of histopathological changes in the nasal cavity. Evidence presented of some transiently increased cell proliferation at lower concentrations]	Zwart et al., 1988
Groups of 25 male Wistar rats exposed to 0, 1, or 2 ppm (0, 1.2, or 2.4 mg/m ³) formaldehyde for 8 h/day (continuous exposure) or to 2 or 4 ppm (2.4 or 4.8 mg/m ³) formaldehyde in eight 30-min exposure periods separated by 30-min intervals (intermittent exposure), 5 days/week for 13 weeks.	2.4	4.8	Histopathological effects in nasal cavity. In animals with the same cumulative exposure to formaldehyde (i.e., 19.2 mg/m ³ -h per day), the incidence of substance-related histopathological changes in the respiratory epithelium was increased in animals exposed intermittently to the higher concentration. [these concentrations of formaldehyde had no significant effect upon cell proliferation in the nasal cavity]	Wilmer et al., 1989

Table 6 (contd).

Protocol	Effect levels (mg/m ³)		Critical effect [comments]	Reference
	NO(A)EL	LO(A)EL		
Groups of 10 male F344 rats exposed to 0, 0.7, 2.0, 5.9, 10.5, or 14.5 ppm (0, 0.84, 2.4, 7.1, 12.6, or 17.4 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 11 weeks and 4 days.	2.4	7.1	Histopathological effects and increased cell proliferation in nasal cavity.	Casanova et al., 1994
Chronic toxicity				
Groups of cynomolgus monkeys (6 male), rats (20 male and female), and hamsters (10 male and female) exposed to 0, 0.2, 1, or 3 ppm (0, 0.24, 1.2, or 3.6 mg/m ³) formaldehyde for 22 h/day, 7 days/week, for 26 weeks.	1.2	3.6	Monkeys and rats (histopathological effects in nasal cavity). Comparable effects observed in both species.	Rusch et al., 1983
Groups of approximately 120 male and female F344 rats and B6C3F ₁ mice exposed to 0, 2.0, 5.6, or 14.3 ppm (0, 2.4, 6.7, or 17.2 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for up to 24 months, followed by an observation period of 6 months.	2.4 (mice)	2.4 (rats)	Rats and mice (histopathological effects in nasal cavity).	Swenberg et al., 1980; Kerns et al., 1983
Groups of 10 male Wistar rats exposed to 0, 0.1, 1.0, or 9.4 ppm (0, 0.12, 1.2, or 11.3 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 52 weeks.	1.2	11.3	Histopathological effects in nasal cavity.	Appelman et al., 1988
Groups of 30 male Wistar rats exposed to 0, 0.1, 1, or 9.8 ppm (0, 0.12, 1.2, or 11.8 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 28 months.	1.2	11.8	Histopathological effects in nasal cavity.	Woutersen et al., 1989
Groups of 30 Wistar rats exposed to 0, 0.1, 1, or 9.2 ppm (0, 0.12, 1.2, or 11.0 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for 3 months and then observed for a further 25-month period.	1.2	11.0	Histopathological effects in nasal cavity. [relatively short period of exposure to formaldehyde]	Woutersen et al., 1989
Groups of approximately 90–150 male F344 rats exposed to 0, 0.7, 2, 6, 10, or 15 ppm (0, 0.84, 2.4, 7.2, 12, or 18 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for up to 24 months.	2.4	7.2	Histopathological effects and increased cell proliferation in nasal cavity.	Monticello et al., 1996
Groups of 32 male F344 rats exposed to 0, 0.3, 2.17, or 14.85 ppm (0, 0.36, 2.6, or 17.8 mg/m ³) formaldehyde for 6 h/day, 5 days/week, for up to 28 months.	0.36	2.6	Histopathological effects in nasal cavity. [incidence summed for all animals examined during interim and terminal sacrifices]	Kamata et al., 1997

Table 7: Summary of non-neoplastic effect levels (oral exposure) for formaldehyde in animals.

Protocol	Effect levels (mg/kg body weight per day)		Critical effect [comments]	Reference
	NOEL	LO(A)EL		
Short-term toxicity				
Groups of 10 male and female Wistar rats administered drinking-water containing amounts of formaldehyde estimated sufficient to provide target intakes of 0, 5, 25, or 125 mg/kg body weight per day for 4 weeks.	25	125	Histopathological effects in the forestomach and increase in relative kidney weight. [exposure to formaldehyde had no effect upon the morphology of the liver or kidneys]	Til et al., 1988
Subchronic toxicity				
Groups of 15 male and female Sprague-Dawley rats administered drinking-water containing amounts of formaldehyde estimated sufficient to achieve target doses of 0, 50, 100, or 150 mg/kg body weight per day for 13 weeks.	50	100	Reduction in weight gain. [exposure to formaldehyde had no effect on the blood or urine and produced no histopathological changes in internal organs (including the gastrointestinal mucosa); limited number of end-points examined; target intakes may not have been achieved]	Johannsen et al., 1986
Groups of four male and female beagle dogs administered diets containing solutions of formaldehyde in amounts estimated sufficient to achieve target doses of 0, 50, 75, or 100 mg/kg body weight per day for 90 days.	75	100	Reduction in weight gain. [exposure to formaldehyde had no effect upon haematological or clinical parameters or organ histopathology (including the gastrointestinal mucosa); limited number of end-points examined; target intakes may not have been achieved]	Johannsen et al., 1986
Chronic toxicity				
Groups of 70 male and female Wistar rats administered drinking-water containing formaldehyde adjusted to achieve target intakes ranging from 0 to 125 mg/kg body weight per day for up to 2 years. [The average concentration of formaldehyde in the drinking-water was 0, 20, 260, or 1900 mg/litre in the control, low-, mid-, and high-dose groups, respectively.]	15	82	Histopathological effects in the forestomach and glandular stomach. Reduced weight gain. [exposure to formaldehyde had no effect upon haematological parameters]	Til et al., 1989
Groups of 20 male and female Wistar rats administered drinking-water containing 0, 0.02%, 0.1%, or 0.5% (0, 200, 1000, or 5000 mg/litre) formaldehyde for 24 months (for approximate intakes of 0, 10, 50, and 300 mg/kg body weight per day, respectively).	10	300	Reduced weight gain, altered clinical chemistries, and histopathological effects in the forestomach and glandular stomach. [small group sizes]	Tobe et al., 1989



■ Monticello et al. (1996) ■ Tobe et al. (1985) ■ Sellakumar et al. (1985) ■ Kerns et al. (1983) ■ Kamata et al. (1997)

Figure 1: Formaldehyde carcinogenicity.

weight per day; no-observed-effect levels (NOELs) were 50 and 75 mg/kg body weight per day, respectively.

8.3 Long-term exposure and carcinogenicity

8.3.1 Long-term exposure

The principal non-neoplastic effects in animals exposed to formaldehyde by inhalation are histopathological changes (e.g., squamous metaplasia, basal hyperplasia, rhinitis) within the nasal cavity and upper respiratory tract. Most chronic inhalation toxicity studies have been conducted in rats, with the development of histopathological effects in the nasal cavity being observed at concentrations of formaldehyde of 2 ppm (2.4 mg/m³) and higher (Swenberg et al., 1980; Kerns et al., 1983; Rusch et al., 1983; Appelman et al., 1988; Woutersen et al., 1989; Monticello et al., 1996). The principal non-neoplastic effect in animals exposed orally to formaldehyde is the development of histopathological changes within the forestomach and glandular stomach, with effects in rats at 82 mg/kg body weight per day and above (Til et al., 1989; Tobe et al., 1989).

8.3.2 Carcinogenicity

An increased incidence of tumours in the nasal cavity was observed in five investigations in which rats were exposed via inhalation to concentrations of formaldehyde greater than 6.0 ppm (7.2 mg/m³). Currently, there is no definitive evidence indicating that formaldehyde is carcinogenic when administered orally to laboratory animals. Chronic dermal toxicity studies (Krivanek et al., 1983; Iversen, 1988) and older inves-

tigations in which animals were injected with formaldehyde (IPCS, 1989) add little additional weight to the evidence for the carcinogenicity of formaldehyde in animals.

8.3.2.1 Inhalation

The results of carcinogenesis bioassays by the inhalation route in rats in which there were increases in nasal tumour incidence are presented in Figure 1. Exposure-response in these investigations was similar and highly non-linear, with sharp increases in tumour incidence in the nasal cavity occurring only at concentrations greater than 6 ppm (7.2 mg/m³) formaldehyde. The most extensive bioassay conducted to date in which proliferative responses in the epithelium of various regions of the nasal cavity were investigated is that by Monticello et al. (1996).

In a study in which groups of male and female F344 rats were exposed to 0, 2.0, 5.6, or 14.3 ppm (0, 2.4, 6.7, or 17.2 mg/m³) formaldehyde for 6 h/day, 5 days/week, for up to 24 months, followed by an observation period of 6 months, the incidence of squamous cell carcinoma in the nasal cavity was markedly increased only in the high-concentration groups compared with the unexposed controls. The incidence of this tumour was 0/118, 0/118, 1/119 (1%), and 51/117 (44%) in males and 0/118, 0/118, 1/116 (1%), and 52/119 (44%) in females in the control, low-, mid-, and high-concentration groups, respectively (Kerns et al., 1983). Precise histopathological analysis revealed that in animals exposed to the highest concentration of formaldehyde, more than half of the nasal squamous tumours were located on the lateral side of the nasal turbinate and adjacent lateral wall at the

front of the nose (Morgan et al., 1986c). Two nasal carcinomas (in male and female rats) and two undifferentiated carcinomas or sarcomas (in male rats) were also observed in animals from the high-concentration groups.

In a follow-up study, Monticello et al. (1996) exposed male F344 rats to 0, 0.7, 2, 6, 10, or 15 ppm (0, 0.84, 2.4, 7.2, 12, or 18 mg/m³) formaldehyde for 6 h/day, 5 days/week, for up to 24 months. Epithelial cell proliferation at seven sites within the nasal cavity (e.g., anterior lateral meatus, posterior lateral meatus, anterior mid-septum, posterior mid-septum, anterior dorsal septum, medial maxilloturbinate, and maxillary sinus) was determined after 3, 6, 12, and 18 months of exposure. The overall incidence of nasal squamous cell carcinoma in animals exposed to 0, 0.7, 2, 6, 10, or 15 ppm (0, 0.84, 2.4, 7.2, 12, or 18 mg/m³) formaldehyde was 0/90, 0/90, 0/90, 1/90 (1%), 20/90 (22%), and 69/147 (47%), respectively. Tumours were located primarily in the anterior lateral meatus, the posterior lateral meatus, and the mid-septum.

In a more limited study in which dose–response was not examined, Sellakumar et al. (1985) exposed male Sprague-Dawley rats to 0 or 14.8 ppm (0 or 17.8 mg/m³) formaldehyde for 6 h/day, 5 days/week, for approximately 2 years. These authors reported a marked increase in the incidence of nasal squamous cell carcinoma — 0/99 and 38/100 in the control and formaldehyde-exposed animals, respectively. These tumours were considered to have arisen primarily from the nasomaxillary turbinates and nasal septum. An increase in the incidence of nasal squamous cell carcinoma was also reported in a study by Tobe et al. (1985), in which groups of male F344 rats were exposed to formaldehyde at 0, 0.3, 2, or 14 ppm (0, 0.36, 2.4, or 17 mg/m³) for 6 h/day, 5 days/week, for 28 months. Fourteen of 32 animals in the high-concentration group (i.e., 44%) developed nasal squamous cell carcinoma, compared with none in the unexposed (control), low-, or mid-concentration groups. In another study in which male F344 rats were exposed to 0, 0.3, 2.2, or 14.8 ppm (0, 0.36, 2.6, or 17.8 mg/m³) formaldehyde for 6 h/day, 5 days/week, for up to 28 months, an increased incidence of nasal squamous cell carcinoma was observed in the high-concentration group (Kamata et al., 1997); the overall incidence of nasal tumours among these formaldehyde-exposed animals, dead or sacrificed after 12, 18, 24, and 28 months on study, was 13/32 (41%), compared with 0/32 and 0/32 in two groups of unexposed controls.

Compared with unexposed controls, the incidence of nasal squamous cell carcinoma was not significantly increased in male Wistar rats exposed to formaldehyde at concentrations of 0.1, 1, or 9.8 ppm (0.12, 1.2, or 11.8 mg/m³) for 6 h/day, 5 days/week, for 28 months (i.e., 0% and 4% of the controls and animals exposed to 9.8 ppm [11.8 mg/m³], respectively, had nasal squamous cell carcinomas) (Woutersen et al., 1989). However, consistent with the hypothesized role of tissue damage in formalde-

hyde-induced nasal tumours, when animals with noses damaged by electrocoagulation were similarly exposed, the incidence of this tumour type was markedly increased in the high-concentration group (i.e., 1/54, 1/58, 0/56, and 15/58 in animals exposed to 0, 0.1, 1, or 9.8 ppm [0, 0.12, 1.2, or 11.8 mg formaldehyde/m³], respectively) (Woutersen et al., 1989).

In other studies in rats, a small but not statistically significant increase in the incidence of tumours of the nasal cavity was observed in animals exposed daily to 20 ppm (24 mg/m³) formaldehyde for 13 weeks and then observed until 130 weeks (Feron et al., 1988), but not in animals exposed to 9.4 ppm (11.3 mg/m³) formaldehyde for 52 weeks (Appelman et al., 1988) or to 12.4 ppm (14.9 mg/m³) formaldehyde for 104 weeks (in either the presence or absence of wood dust at a concentration of 25 mg/m³) (Holmström et al., 1989a). The lack of observed statistically significant increases in tumour incidence in these investigations may be a function of small group sizes and/or short periods of exposure.

In a study in which groups of male and female B6C3F₁ mice were exposed to 0, 2.0, 5.6, or 14.3 ppm (0, 2.4, 6.7, or 17.2 mg/m³) formaldehyde for 6 h/day, 5 days/week, for up to 24 months, followed by an observation period of 6 months, there were no statistically significant increases in the incidence of nasal cavity tumours, compared with unexposed controls (Kerns et al., 1983). After 24 months' exposure to formaldehyde, two male mice in the high-concentration group developed squamous cell carcinoma in the nasal cavity. The incidence of lung tumours was not increased in an early study in which groups of 42–60 C3H mice (sex not specified) were exposed to formaldehyde at concentrations of 0, 42, 83, or 167 ppm (0, 50, 100, or 200 mg/m³) for three 1-h periods per week for 35 weeks, although, due to high mortality, treatment in the high-dose group was discontinued in the 4th week, and there was no evaluation of the nasal tissues (Horton et al., 1963). Compared with 132 unexposed controls, there was no increase in the incidence of respiratory tract tumours in 88 male Syrian hamsters exposed to 10 ppm (12 mg/m³) formaldehyde for their entire lives (Dalbey, 1982).

8.3.2.2 Oral exposure

In the most comprehensive study identified in male and female Wistar rats administered drinking-water containing formaldehyde in amounts estimated to achieve target intakes ranging up to 125 mg/kg body weight per day for up to 2 years, there was no significant increase in tumour incidence compared with unexposed controls (Til et al., 1989). Tobe et al. (1989) also reported, although data were not presented, that, compared with unexposed controls, tumour incidence was not increased in small groups of male and female Wistar rats administered drinking-water containing up to 5000 mg formaldehyde/litre (i.e., providing intakes up to 300 mg/kg body weight per day).

In contrast, increases in tumours of the haematopoietic system were reported by Soffritti et al. (1989), based upon the results of a study in which Sprague-Dawley rats were administered drinking-water containing formaldehyde at concentrations ranging from 0 to 1500 mg/litre for 104 weeks and the animals observed until death (estimated intakes up to approximately 200 mg/kg body weight per day). The proportion of males and females with leukaemias (all “haemolymphoreticular neoplasias,” e.g., lymphoblastic leukaemias and lymphosarcomas, immunoblastic lymphosarcomas, and “other” leukaemias) increased from 4% and 3%, respectively, in the controls to 22% and 14%, respectively, in the animals receiving drinking-water containing 1500 mg formaldehyde/litre. Compared with unexposed controls, there was no dose-related increase in the incidence of stomach tumours in animals receiving formaldehyde. Limitations of this study include the “pooling” of tumour types, the lack of statistical analysis, and limited examination of non-neoplastic end-points. Parenthetically, it should be noted that the incidence of haematopoietic tumours (e.g., myeloid leukaemia, generalized histiocytic sarcoma) was not increased in Wistar rats receiving up to 109 mg formaldehyde/kg body weight per day in drinking-water for up to 2 years (Til et al., 1989).

8.4 Genotoxicity and related end-points

A wide variety of end-points have been assessed in *in vitro* assays of the genotoxicity of formaldehyde (see IARC, 1995, for a review). Generally, the results of these studies have indicated that formaldehyde is genotoxic in both bacterial and mammalian cells *in vitro* (inducing both point and large-scale mutations) (IARC, 1995). Formaldehyde induces mutations in *Salmonella typhimurium* and in *Escherichia coli*, with positive results obtained in the presence or absence of metabolic activation systems. Formaldehyde increases the frequency of chromatid/chromosome aberrations, sister chromatid exchange, and gene mutations in a variety of rodent and human cell types. Exposure to formaldehyde increased DNA damage (strand breaks) in human fibroblasts and rat tracheal epithelial cells and increased unscheduled DNA synthesis in rat nasoturbinates and maxilloturbinates cells.

As most formaldehyde is deposited and absorbed in regions with which it first comes into contact, genotoxic effects at distal sites following inhalation or ingestion might not be expected. Exposure of male Sprague-Dawley rats to 0.5, 3, or 15 ppm (0.6, 3.6, or 18 mg/m³) formaldehyde for 6 h/day, 5 days/week, for 1 or 8 weeks had no effect upon the proportion of bone marrow cells with cytogenetic anomalies (e.g., chromatid or chromosome breaks, centric fusions) compared with unexposed controls, although animals in the group exposed to the highest concentration had a modest (1.7- to 1.8-fold),

statistically significant (i.e., $P < 0.05$) increase in the proportion of pulmonary macrophage with chromosomal aberrations compared with controls (approximately 7% and 4%, respectively) (Dallas et al., 1992). However, Kitaeva et al. (1990) observed a statistically significant increase in the proportion of bone marrow cells with chromosomal aberrations (chromatid or chromosome breaks) from female Wistar rats exposed to low concentrations of formaldehyde for 4 h/day for 4 months — approximately 0.7%, 2.4%, and 4% in animals exposed to 0, 0.42, or 1.3 ppm (0, 0.5, or 1.5 mg/m³), respectively. In older studies, exposure of male and female F344 rats to approximately 0.5, 5.9, or 14.8 ppm (0.6, 7.1, or 17.8 mg/m³) formaldehyde for 6 h/day for 5 consecutive days had no effect upon the frequency of sister chromatid exchange or chromosomal aberrations and mitotic index in blood lymphocytes (Kligerman et al., 1984). Statistically significant ($P < 0.05$) increases in the proportion of cells with micronuclei and nuclear anomalies (e.g., karyorrhexis, pyknosis, vacuolated bodies) were observed in the stomach, duodenum, ileum, and colon within 30 h of administration (by gavage) of 200 mg formaldehyde/kg body weight to male Sprague-Dawley rats (Migliore et al., 1989). No significant evidence of genotoxicity (e.g., micronuclei, chromosomal aberrations) in bone marrow cells, splenic cells, or spermatocytes was reported in earlier studies in which various strains of mice were injected intraperitoneally with formaldehyde (Fontignie-Houbrechts, 1981; Gocke et al., 1981; Natarajan et al., 1983).

The mutational profile for formaldehyde varies among cell types and concentration of formaldehyde to which the cells were exposed *in vitro* and includes both point and large-scale changes. In human lymphoblasts, about half of the mutants at the X-linked *hprt* locus had deletions of some or all of the *hprt* gene bands; the other half were assumed to have point mutations (Crosby et al., 1988). In a subsequent study, six of seven formaldehyde-induced mutants with normal restriction fragment patterns had point mutations at AT sites, with four of these six occurring at one specific site (Liber et al., 1989). Crosby et al. (1988) also examined the mutational spectra induced by formaldehyde at the *gpt* gene in *E. coli* (Crosby et al., 1988). A 1-h exposure to 4 mmol formaldehyde/litre induced a spectrum of mutants that included large insertions (41%), large deletions (18%), and point mutations (41%), the majority of which were transversions occurring at GC base pairs. Increasing the concentration of formaldehyde to 40 mmol/litre resulted in a much more homogeneous spectrum, with 92% of the mutants being produced by a point mutation, 62% of which were transitions at a single AT base pair. In contrast to these findings, when naked plasmid DNA containing the *gpt* gene was treated with formaldehyde and shuttled through *E. coli*, most of the mutations were found to be frameshifts.

8.5 Reproductive toxicity

Other than a significant ($P < 0.01$) weight loss in the dams and a 21% reduction in the mean weight of the fetuses from dams in the highest concentration group, the exposure of pregnant Sprague-Dawley rats to 0, 5.2, 9.9, 20, or 39 ppm (0, 6.2, 11.9, 24.0, or 46.8 mg/m³) formaldehyde for 6 h/day from days 6 through 20 of gestation had no effect upon the mean number of live fetuses, resorptions, and implantation sites or fetal losses per litter; although the occurrence of missing sternebra and delayed ossification of the thoracic vertebra were increased in fetuses from the highest exposure group, the increases were neither statistically significant (i.e., $P > 0.05$) nor concentration dependent (Saillenfait et al., 1989).

Similarly, although weight gain was significantly ($P < 0.05$) reduced in dams exposed to the highest concentration, exposure of pregnant Sprague-Dawley rats to approximately 2, 5, or 10 ppm (2.4, 6, or 12 mg/m³) formaldehyde for 6 h/day on days 6 through 15 of gestation had no substance-related effect upon the number of fetuses with major malformations or skeletal anomalies; reduced ossification of the pubic and ischial bones in fetuses from dams exposed to the two highest concentrations of formaldehyde was attributed to larger litter sizes and small fetal weights. Indices of embryotoxicity (e.g., number of corpora lutea, implantation sites, live fetuses, resorptions, etc.) were not affected by exposure to formaldehyde (Martin, 1990).

8.6 Immunological effects and sensitization

Other than a significant ($P < 0.05$) 9% increase in bacterial pulmonary survival in one study of mice exposed to 15 ppm (18 mg/m³) (Jakab, 1992), as well as a statistically significant ($P \neq 0.05$ or 0.01) reduction in serum IgM titres in animals orally administered 40 or 80 mg/kg body weight per day, 5 days/week, for 4 weeks (Vargová et al., 1993), adverse effects on either cell- or humoral-mediated immune responses have generally not been observed in rats or mice exposed to formaldehyde (Dean et al., 1984; Adams et al., 1987; Holmström et al., 1989b). End-points examined in these studies (Dean et al., 1984; Adams et al., 1987; Holmström et al., 1989b) included splenic or thymic weights, bone marrow cellularity, the proportion of splenic B- and T-cells, NK-cell activity, lymphocyte proliferation, the number, function, or maturation of peritoneal macrophages, host resistance to bacterial or tumour challenge, and B-cell function through induction of (IgG and IgM) antibodies, with exposures ranging from 1 to 15 ppm (1.2 to 18 mg/m³) formaldehyde.

Results of studies in laboratory animals have indicated that formaldehyde may enhance their sensitization to inhaled allergens. In female BALB/c mice sensitized to ovalbumin, the serum titre of IgE anti-ovalbumin antibodies was increased approximately 3-fold in animals pre-exposed to 2.0 mg formaldehyde/m³ for 6 h/day on 10 consecutive days (Tarkowski & Gorski, 1995). Similarly, exposure of female Dunkin-Hartley guinea-pigs, sensitized to airborne ovalbumin, to 0.3 mg formaldehyde/m³ produced a significant ($P < 0.01$) 3-fold increase in bronchial sensitization, as well as a significant ($P < 0.05$) 1.3-fold increase in serum anti-ovalbumin antibodies (Riedel et al., 1996).

8.7 Mode of action

The mechanisms by which formaldehyde induces tumours in the 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 ppm (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 & Heck, 1987). This correlates with the non-linear increase in DNA-protein crosslink formation at exposures above this level.

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 end-points (DNA-protein crosslinking, sustained increases in proliferation, and tumours) and concordance of incidence of these effects across regions of the nasal passages (Table 8).

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-, medium-, and long-term 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 ppm (#2.4 mg/m³) 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

Table 8: Comparative effects of formaldehyde exposure upon cell proliferation, DNA–protein crosslinking, and tumour incidence.

Formaldehyde concentration, mg/m ³ (ppm)	Cell proliferation (³ H]thymidine-labelled cells/mm basement membrane) ^a			DNA–protein crosslink formation (pmol [¹⁴ C]formaldehyde bound/mg DNA) ^b		Incidence of nasal carcinoma ^c			
	Anterior lateral meatus	Posterior lateral meatus	Anterior mid-septum	“high tumour region”	“low tumour region”	All sites	Anterior lateral meatus	Posterior lateral meatus	Anterior mid-septum
0 (0)	10.11	7.69	6.58	0	0	0/90	0/90	0/90	0/90
0.84 (0.7)	10.53	7.82	8.04	5	5	0/90	0/90	0/90	0/90
2.4 (2)	9.83	11.24	12.74	8	8	0/96	0/96	0/96	0/96
7.2 (6)	15.68	9.96	4.15	30	10	1/90	1/90	0/90	0/90
12 (10)	76.79	15.29	30.01	–	–	20/90	12/90	2/90	0/90
18 (15)	93.22	59.52	75.71	150	60	69/147	17/147	9/147	8/147

^a Cell proliferation measured in three locations of the nasal epithelium in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 h/day, 5 days/week, for 3 months (Monticello et al., 1996).

^b Extent of DNA–protein crosslink formation measured in two regions of the nasal cavity (respiratory mucosa) in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 h/day, 5 days/week, for about 12 weeks; the complete lateral meatus was designated the “high tumour region”; the “low tumour region” comprised the medial aspects of naso- and maxilloturbinates, posterior lateral wall, posterior dorsal septum excluding olfactory region, and nasopharyngeal meatuses (Casanova et al., 1994). Data were derived from graphical representations in the reference cited.

^c Incidence of nasal tumours within the entire nasal cavity or the anterior lateral meatus, posterior lateral meatus, or anterior mid-septum in male F344 rats exposed to the indicated concentrations of formaldehyde, 6 h/day, 5 days/week, for 24 months (Monticello et al., 1996).

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 & 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).

It is the interaction with the genome at the site of first contact, however, that is of greatest interest with respect to the carcinogenicity of formaldehyde (i.e., in the induction of nasal tumours in rats). Formaldehyde-induced DNA-protein crosslinking has been observed in the nasal epithelium of rats (Casanova & Heck, 1987; Heck & Casanova, 1987; Casanova et al., 1989, 1994), as well as in epithelia lining the respiratory tract of monkeys (Casanova et al., 1991) exposed via inhalation. DNA-protein crosslinks are considered a marker of mutagenic potential, since they may initiate DNA replication errors, resulting in mutation. The exposure-response relationship is highly non-linear, with a sharp increase in DNA-protein crosslinking at concentrations above 4 ppm (4.8 mg/m³) formaldehyde (see also Table 8) without accumulation on repeated exposure (Casanova et al., 1994). Formaldehyde has also induced the formation of DNA-protein crosslinks in a variety of human and rat cell types (Saladino et al., 1985; Bermudez & Delehanty, 1986; Snyder & van Houten, 1986; Craft et al., 1987; Heck & Casanova, 1987; Cosma et al., 1988; Olin et al., 1996). In 5 of 11 squamous cell carcinomas from rats exposed to 15 ppm (18 mg/m³) for up to 2 years, there were point mutations at the GC base pairs in the p53 cDNA sequence (Recio et al., 1992).

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 short- and medium-term 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.

9. EFFECTS ON HUMANS

9.1 Case reports and clinical studies

Reports of death following acute inhalation exposure to formaldehyde were not identified. Ulceration and damage along the aerodigestive tract, including oral and gastrointestinal mucosa, have been observed in cases where formaldehyde had been ingested (Kochhar et al., 1986; Nishi et al., 1988; IPCS, 1989). There are frequent reports on cases of systemic (e.g., anaphylaxis) or more often localized (e.g., contact dermatitis) allergic reactions attributed to the formaldehyde (or formaldehyde-containing resins) present in household and personal care (and dental) products, clothing and textiles, bank note paper, and medical treatments and devices (Maurice et al., 1986; Feinman, 1988; Ebner & Kraft, 1991; Norton, 1991; Flyvholm & Menné, 1992; Fowler et al., 1992; Ross et al., 1992; Vincenzi et al., 1992; Bracamonte et al., 1995; El Sayed et al., 1995; Wantke et al., 1995).

In a number of clinical studies, generally mild to moderate sensory eye, nose, and throat irritation was experienced by volunteers exposed for short periods to levels of formaldehyde ranging from 0.25 to 3.0 ppm (0.30 to 3.6 mg/m³) (Andersen & Mølhav, 1983; Sauder et al., 1986, 1987; Schachter et al., 1986; Green et al., 1987, 1989; Witek et al., 1987; Kulle, 1993; Pazdrak et al., 1993). Mucociliary clearance in the anterior portion of the nasal cavity was reduced following exposure of volunteers to 0.25 ppm (0.30 mg/m³) formaldehyde (Andersen & Mølhav, 1983). Based upon the results of experimental studies, it appears that in healthy individuals as well as those with asthma, brief exposure (up to 3 h) to concentrations of formaldehyde up to 3.0 ppm (3.6 mg/m³) had no significant clinically detrimental effect upon lung function (Day et al., 1984; Sauder et al., 1986, 1987; Schachter et al., 1986, 1987; Green et al., 1987; Witek et al., 1987; Harving et al., 1990).

9.2 Epidemiological studies

9.2.1 Cancer

Possible associations between formaldehyde and cancers of various organs have been examined extensively in epidemiological studies in occupationally exposed populations. Indeed, there have been over 30 cohort and case-control studies of professionals, including pathologists and embalmers, and industrial workers. In addition, several authors have conducted meta-analyses of the available data.

Relevant risk measures from recent case-control and cohort studies are presented in Tables 9 and 10, respectively.

In most epidemiological studies, the potential association between exposure to formaldehyde and cancer of the respiratory tract has been examined. However, in some case-control and cohort studies, increased risks of various non-respiratory tract cancers (e.g., multiple myeloma, non-Hodgkin's lymphoma, ocular melanoma, brain, connective tissue, pancreatic, leukaemic, lymphoid and haematopoietic, colon) have occasionally been observed. However, such increases have been reported only sporadically, with little consistent pattern. Moreover, results of toxicokinetic and metabolic studies in laboratory animals and humans indicate that most inhaled formaldehyde is deposited within the upper respiratory tract. Available evidence for these tumours at sites other than the respiratory tract does not, therefore, fulfil traditional criteria of causality (e.g., consistency, biological plausibility) for associations observed in epidemiological studies, and the remainder of this section addresses the tumours for which the weight of evidence is greatest — initially nasal and, subsequently, lung.

In case-control studies (see Table 9), while sometimes no increase was observed overall (Vaughan et al., 1986a), significantly increased risks of nasopharyngeal cancer (up to 5.5-fold) were observed among workers with 10–25 years of exposure or in the highest exposure category in three out of four investigations (Vaughan et al., 1986a; Roush et al., 1987; West et al., 1993), although there were limitations associated with most of these studies, as noted in Table 9. There was no increase in nasopharyngeal cancers in an additional investigation that is also considered to be limited (Olsen & Asnaes, 1986). In three studies in which the association between formaldehyde and nasal squamous cell carcinomas was examined, there were non-significant increases in two (Olsen & Asnaes, 1986; Hayes et al., 1990) and no increase in another (Luce et al., 1993), although there were limitations (as noted in Table 9) associated with all of these investigations. In the only investigation in which the association between exposure to formaldehyde and adenocarcinoma of the nasal cavity was examined, there was a non-significant increase that was exacerbated in the presence of wood dust (Luce et al., 1993), although possible residual confounding by wood dust exposure could not be excluded.

There is little convincing evidence of increased risks of nasopharyngeal cancer in cohort studies of populations of professionals or industrial workers occupa-

tionally exposed to formaldehyde, although it should be noted that the total number of cases of this rare cancer in all of the studies was small (approximately 15 cases in all studies in Table 10, with some overlap). Risks were not increased in smaller studies of anatomists or mortuary workers (Hayes et al., 1990) or in an investigation of proportionate incidence in industrial workers (Hansen & Olsen, 1995); in the latter study, however, the standardized proportionate incidence ratio for cancers of the “nasal cavity” was significantly increased (3-fold) in more exposed workers. In a cohort of 11 000 garment workers, the number of deaths due to cancer of the nasal cavity was considered too small to evaluate (Stayner et al., 1988). In a cohort of 14 000 workers employed in six chemical and plastic factories in the United Kingdom for which 35% of the cohort was exposed to >2 ppm (>2.4 mg/m³), only one nasal cancer was observed versus 1.7 expected (Gardner et al., 1993). The results of the largest industrial cohort mortality study of 26 561 workers first employed before 1966 at 10 plants in the USA (4% of cohort exposed to \$2 ppm [2.4 mg/m^3]) indicated an approximately 3-fold excess of deaths due to nasopharyngeal cancer associated with occupational exposure to formaldehyde (Blair et al., 1986). However, subsequent analyses revealed that five of the seven observed deaths were among individuals who had also been exposed to particulates; four of the seven observed deaths occurred at one specific industrial plant (Blair et al., 1987; Collins et al., 1988; Marsh et al., 1996). Three of the seven observed deaths due to nasopharyngeal cancer occurred in individuals with less than 1 year of employment (Collins et al., 1988), and the four deaths at one specific plant occurred equally in both short-term and long-term workers (Marsh et al., 1996).

In most case-control studies, there have been no increases in lung cancer (Bond et al., 1986; Gérin et al., 1989; Brownson et al., 1993; Andjelkovich et al., 1994). In the single study where exposure-response was examined, there was no significant increase in adenocarcinoma of the lung for those with “long-high” occupational exposure; although the odds ratio was greater than for “lung cancer,” the number of cases on which this observation was based was small (Gérin et al., 1989). There was no association of relative risks (RR) with latency period (Andjelkovich et al., 1994). In the most extensive investigation of exposure-response, there were no increases in lung cancer in workers subdivided by latency period, although there was a non-significant increase for those co-exposed to wood dust. There was no statistically significant increased risk for “all respiratory cancer” by level, duration, cumulative exposure, duration of repeated exposures to peak levels, or dura-

Table 9: Summary of risk measures from case-control studies.

Cancer/ Study population	Formaldehyde exposure	Risk measure (95% CI)	Reference (comments)
Oropharynx or hypopharynx SEER ^a population based – Washington State	\$10 years occupational exposure occupational exposure score ^b of \$20	OR = 1.3 (0.7–2.5) OR = 1.5 (0.7–3.0)	Vaughan et al., 1986a (IARC Working Group noted that different proportions of interviews conducted with next-of-kin cases and controls may have affected odds ratios)
Nasopharynx SEER population based – Washington State, USA	exposure score ^b of \$20	OR = 2.1 (0.6–7.8)	Vaughan et al., 1986a (IARC Working Group noted that different proportions of interviews conducted with next-of-kin cases and controls may have affected odds ratios)
Nasopharynx SEER population based – Washington State, USA	residential exposure of \$10 years residential exposure of <10 years	OR = 5.5 (1.6–19.4) OR = 2.1 (0.7–6.6)	Vaughan et al., 1986b (IARC Working Group considered living in a mobile home a poor proxy for exposure)
Nasal squamous cell carcinoma Hospital based – Netherlands	“any” occupational exposure; assessment A “any” occupational exposure; assessment B	OR = 3.0 (1.3–6.4) ^c OR = 1.9 (1.0–3.6) ^c	Hayes et al., 1986 (IARC Working Group noted that a greater proportion of cases than controls were dead and variable numbers of next-of-kin were interviewed, 10% of controls but none of cases, by telephone; noted also that, although different, results for exposure assessments A & B ^d were both positive)
Squamous cell carcinoma of nasal cavity/paranasal sinus Danish Cancer Registry	occupational exposure without exposure to wood dust	OR = 2.0 (0.7–5.9)	Olsen & Asnaes, 1986 (IARC Working Group noted possibly incomplete adjustment for confounding for wood dust for adenocarcinoma; felt that squamous cell carcinoma less likely to be affected, since no clear association with wood dust) (Small number of cases)
Nasopharynx Connecticut Tumour Registry, USA	highest potential exposure category highest potential exposure category and dying at 68+ years of age	OR = 2.3 (0.9–6.0) OR = 4.0 (1.3–12)	Roush et al., 1987
Oral/oropharynx Population based – Turin, Italy	“any” occupational exposure “probable or definite” occupational exposure	OR = 1.6 (0.9–2.8) OR = 1.8 (0.6–5.5)	Merletti et al., 1991
Larynx SEER population based – Washington State, USA	“high” occupational exposure occupational exposure of \$10 years occupational exposure score ^b of \$20	OR = 2.0 (0.2–19.5) OR = 1.3 (0.6–3.1) OR = 1.3 (0.5–3.3)	Wortley et al., 1992
Nasal cavity/paranasal sinus (squamous cell carcinoma) Population based – France	males with possible exposure to formaldehyde males with duration of exposure: #20 years >20 years	OR = 0.96 (0.38–2.42) OR = 1.09 (0.48–2.50) OR = 0.76 (0.29–2.01)	Luce et al., 1993 (IARC Working Group noted possible residual confounding by exposure to wood dust)
Nasopharynx Hospital based – Philippines	<15 years of exposure >25 years since first exposure <25 years of age at first exposure	OR = 2.7 (1.1–6.6) OR = 2.9 (1.1–7.6) OR = 2.7 (1.1–6.6)	West et al., 1993 (IARC Working Group noted no control for the presence of Epstein-Barr viral antibodies, for which previous strong association with nasopharyngeal cancer was observed)
Lung Nested – cohort of chemical workers – Texas, USA	likely occupational exposure	OR = 0.62 (0.29–1.36)	Bond et al., 1986
Lung Population based – Montreal, Quebec, Canada	“long–high” occupational exposure (cancer controls/ population controls)	OR = 1.5 (0.8–2.8)/ OR = 1.0 (0.4–2.4)	Gérin et al., 1989

Table 9 (contd).

Cancer/ Study population	Formaldehyde exposure	Risk measure (95% CI)	Reference (comments)
Lung (adenocarcinoma) Population based – Montreal, Quebec, Canada	“long–high” occupational exposure (cancer controls/ population controls)	OR = 2.3 (0.9–6.0)/ OR = 2.2 (0.7–7.6)	Gérin et al., 1989
Respiratory cancer Nested – cohort of Finnish woodworkers	cumulative exposure of \$3.6 mg/m ³ - months, without minimum 10-year induction period cumulative exposure of \$3.6 mg/m ³ - months, with minimum 10-year induction period exposure to formaldehyde in wood dust	OR = 0.69 (0.21–2.24) ^c OR = 0.89 (0.26–3.0) ^c OR = 1.19 (0.31–4.56) ^c	Partanen et al., 1990 (IARC Working Group noted that there were too few cancers at sites other than the lung for meaningful analysis)
Lung Population based – Missouri, USA	potentially exposed non-smokers	OR = 0.9 (0.2–3.3)	Brownson et al., 1993
Lung Nested – cohort of US automotive foundry workers	occupational exposure with latency period of: 0 years 10 years 15 years 20 years	OR = 1.31 (0.93–1.85) OR = 1.04 (0.71–1.52) OR = 0.98 (0.65–1.47) OR = 0.99 (0.60–1.62)	Andjelkovich et al., 1994
Multiple myeloma Incident cases in follow- up of cancer prevention study in USA	probably exposed	OR = 1.8 (0.6–5.7)	Boffetta et al., 1989
Multiple myeloma Danish Cancer Registry	males with probable occupational exposure females with probable occupational exposure	OR = 1.1 (0.7–1.6) OR = 1.6 (0.4–5.3)	Heineman et al., 1992; Pottern et al., 1992
Non-Hodgkin’s lymphoma Iowa State Health Registry, USA	potential “lower intensity” of exposure potential “higher intensity” of exposure	OR = 1.2 (0.9–1.7) OR = 1.3 (0.5–3.8)	Blair et al., 1993
Ocular melanoma Cases diagnosed or treated at University of California at San Francisco Ocular Oncology Unit, USA	“ever” exposed to formaldehyde	OR = 2.9 (1.2–7.0)	Holly et al., 1996

^a SEER = Surveillance, Epidemiology and End Results programme of the US National Cancer Institute.

^b Weighted sum of number of years spent in each job, with weighting identical to estimated formaldehyde exposure level for each job.

^c Data in parentheses represent 90% confidence interval.

^d Two independent evaluations of exposure to formaldehyde, designated assessments A and B.

tion of exposure to dust-borne formaldehyde, except in one category (Partanen et al., 1990).

In smaller cohort studies of professional and industrial workers (Table 10), there have been no significant excesses of cancers of the trachea, bronchus, or lung (Hayes et al., 1990; Andjelkovich et al., 1995), the buccal mucosa or pharynx (Matanoski, 1989; Hayes et al., 1990; Andjelkovich et al., 1995), the lung (Stroup et al., 1986; Bertazzi et al., 1989; Hansen & Olsen, 1995), or the respiratory system (Matanoski, 1989). In a cohort of 11 000 garment workers, there was no increase in cancers of the trachea, bronchus, lung, buccal mucosa, or pharynx

(Stayner et al., 1988). In a cohort of 14 000 workers employed at six chemical and plastic factories in the United Kingdom for which 35% of the cohort was exposed to >2 ppm (>2.4 mg/m³), there was a non-significant excess (comparison with local rates) of lung cancers in workers first employed prior to 1965. Among groups employed at individual plants, the standardized mortality ratio for lung cancer was significantly increased only in the “highly exposed” subgroup at one plant. However, there was no significant relationship with years of employment or cumulative exposure (Gardner et al., 1993). There was no

Table 10: Summary of risk measures from cohort studies.

Cohort exposed	Cancer	Risk measure ^a	Reference (comments)
Male anatomists	Brain	SMR = 270 (130–500): 10	Stroup et al., 1986 (Likely exposure to other substances; no quantitative data on exposure)
	Leukaemia	SMR = 150 (70–270): 10	
	“Other lymphatic tissues”	SMR = 200 (70–440): 6	
	Nasal cavity and sinus	SMR = 0 (0–720): 0	
	Larynx	SMR = 30 (0–200): 1	
Male abrasives production workers	Lung	SMR = 30 (1–50): 12	Edling et al., 1987 (Increases based on only two cases each)
	Multiple myeloma	SIR = 4 (0.5–14): 2	
	Lymphoma	SIR = 2 (0.2–7.2): 2	
	Pancreas	SIR = 1.8 (0.2–6.6): 2	
Garment manufacturing workers	Lung	SIR = 0.57 (0.1–2.1): 2	Stayner et al., 1988
	Buccal cavity	SMR = 343 (118–786) ^b : 4	
	Connective tissue	SMR = 364 (123–825) ^b : 4	
	Trachea, bronchus, and lung	SMR = 114 (86–149) ^b : 39	
Resin manufacturing workers	Pharynx	SMR = 111 (20–359) ^b : 2	Bertazzi et al., 1989 (Small cohort exposed primarily to low concentrations; few deaths)
	Alimentary tract	SMR = 134 (<i>P</i> > 0.05): 11	
	Stomach	SMR = 164 (<i>P</i> > 0.05): 5	
	Liver	SMR = 244 (<i>P</i> > 0.05): 2	
Male pathologists	Lung	SMR = 69: 6	Matanoski, 1989
	Buccal cavity and pharynx	SMR = 52 (28–89): 13	
	Respiratory system	SMR = 56 (44–77): 77	
	Hypopharynx	SMR = 470 (97–1340): 3	
	Pancreas	SMR = 140 (104–188): 47	
Male mortuary workers	Leukaemia	SMR = 168 (114–238): 31	Hayes et al., 1990
	Buccal cavity and pharynx	PMR = 120 (81–171): 30	
	Nasopharynx	PMR = 216 (59–554): 4	
	Lymphatic and haematopoietic	PMR = 139 (115–167): 115	
	Colon	115	
Male chemical workers employed before 1965	Trachea, bronchus, and lung	PMR = 127 (104–153): 111	Gardner et al., 1993 (35% of cohort exposed to >2 ppm [$>2.4 \text{ mg/m}^3$])
	Lung	PMR = 94.9: 308	
	Buccal cavity	SMR = 123 (110–136): 348	
	Pharynx	SMR = 137 (28–141): 3 SMR = 147 (59–303): 7	
Workers exposed to >2 ppm ($>2.4 \text{ mg/m}^3$) at one specific plant	Lung	SMR = 126 (107–147): 165	Gardner et al., 1993
Male industrial workers	Lung	SMR = 126 (107–147): 165	Hansen & Olsen, 1995
	Nasal cavity	SPIR = 2.3 (1.3–4.0): 13	
	Nasopharynx	SPIR = 1.3 (0.3–3.2): 4	
	Lung	SPIR = 1.0 (0.9–1.1): 410	
	Larynx	SPIR = 0.9 (0.6–1.2): 32	
Male industrial workers exposed above baseline levels	Oral cavity and pharynx	SPIR = 1.1 (0.7–1.7): 23	Hansen & Olsen, 1995
	Nasal cavity	SPIR = 3.0 (1.4–5.7): 9	
Male automotive foundry workers	Buccal cavity and pharynx	SMR = 131 (48–266): 6	Andjelkovich et al., 1995 (25% of cohort exposed to >1.5 ppm [$>1.8 \text{ mg/m}^3$])
	Trachea, bronchus, and lung	SMR = 120 (89–158): 51	
White male industrial workers exposed to \$0.1 ppm formaldehyde	Nasopharynx	SMR = 270 (<i>P</i> < 0.05): 6	Blair et al., 1986 (4% of cohort exposed to \$2 ppm [$\2.4 mg/m^3])
White male industrial workers with cumulative exposures of:	Nasopharynx	SMR = 270 (<i>P</i> < 0.05): 6	Blair et al., 1986 (4% of cohort exposed to \$2 ppm [$\2.4 mg/m^3])
	0 ppm-years	SMR = 530: 1	
	#0.5 ppm-years	SMR = 271 (<i>P</i> > 0.05): 2	
	0.51–5.5 ppm-years	SMR = 256 (<i>P</i> > 0.05): 2	
>5.5 ppm-years	SMR = 433 (<i>P</i> > 0.05): 2		

Table 10 (contd).

Cohort exposed	Cancer	Risk measure ^a	Reference (comments)
White male industrial workers co-exposed to particulates with cumulative formaldehyde exposures of: 0 ppm-years <0.5 ppm-years 0.5–5.5 ppm-years \$5.5 ppm-years	Nasopharynx	SMR = 0: 0 SMR = 192: 1 SMR = 403: 2 SMR = 746: 2	Blair et al., 1987
White male industrial workers: exposed for <1 year exposed for \$1 year exposed at one plant with particulates	Nasopharynx	SMR = 517 (<i>P</i> # 0.05): 3 SMR = 218 (<i>P</i> > 0.05): 3 SMR = 1031 (<i>P</i> # 0.01): 4	Collins et al., 1988
White male workers, hired between 1947 and 1956, employed at one specific plant for: <1 year \$1 year	Nasopharynx	SMR = 768 (<i>P</i> > 0.05): 2 SMR = 1049 (<i>P</i> < 0.05): 2	Marsh et al., 1996
White male industrial workers exposed to \$0.1 ppm formaldehyde	Lung	SMR = 111 (96–127): 210	Blair et al., 1986 (4% of cohort exposed to \$2 ppm [\$2.4 mg/m ³])
White male industrial workers with \$20 years since first exposure	Lung	SMR = 132 (<i>P</i> # 0.05): 151	Blair et al., 1986 (4% of cohort exposed to \$2 ppm [\$2.4 mg/m ³])
White male industrial workers with cumulative exposures of: 0 ppm-years #0.5 ppm-years 0.51–5.5 ppm-years >5.5 ppm-years	Lung	SMR = 68 (37–113): 14 SMR = 122 (98–150): 88 SMR = 100 (80–124): 86 SMR = 111 (85–143): 62	Blair et al., 1986 (4% of cohort exposed to \$2 ppm [\$2.4 mg/m ³])
Wage-earning white males in industrial cohort exposed to formaldehyde and other substances	Lung	SMR = 140 (<i>P</i> # 0.05): 124	Blair et al., 1990a
Wage-earning white males in industrial cohort exposed to formaldehyde	Lung	SMR = 100 (<i>P</i> > 0.05): 88	Blair et al., 1990a
Subjects in industrial cohort less than 65 years of age with cumulative exposures of: <0.1 ppm-years 0.1–0.5 ppm-years 0.5–2.0 ppm-years >2.0 ppm-years	Lung	RR = 1.0 RR = 1.47 (1.03–2.12) ^b RR = 1.08 (0.67–1.70) ^b RR = 1.83 (1.09–3.08) ^b	Sterling & Weinkam, 1994
Males in industrial cohort less than 65 years of age with cumulative exposures of: <0.1 ppm-years 0.1–0.5 ppm-years 0.5–2.0 ppm-years >2.0 ppm-years	Lung	RR = 1.0 RR = 1.50 (1.03–2.19) ^b RR = 1.18 (0.73–1.90) ^b RR = 1.94 (1.13–3.34) ^b	Sterling & Weinkam, 1994
White wage-earning males in industrial cohort with >2 ppm-years of cumulative exposure and exposure durations of: <1 year 1–5 years 5–10 years >10 years	Lung	SMR = 0: 0 SMR = 110 (<i>P</i> > 0.05): 9 SMR = 280 (<i>P</i> < 0.05): 17 SMR = 100 (<i>P</i> > 0.05): 10	Blair & Stewart, 1994
White male workers employed at one specific plant for: <1 year \$1 year	Lung	SMR = 134 (<i>P</i> < 0.05): 63 SMR = 119 (<i>P</i> > 0.05): 50	Marsh et al., 1996 (25% exposed to >0.7 ppm [>0.84 mg/m ³])
White males in industrial cohort with cumulative exposures of: 0 ppm-years 0.05–0.5 ppm-years 0.51–5.5 ppm-years >5.5 ppm-years	Lung	RR = 1.00 RR = 1.46 (0.81–2.61) RR = 1.27 (0.72–2.26) RR = 1.38 (0.77–2.48)	Callas et al., 1996

^a Unless otherwise noted, values in parentheses are 95% confidence interval or level of statistical significance. Risk measures are presented in the format reported in the references cited. Values in italics are the number of observed deaths or cases, when specified in the reference cited. Abbreviations are as follows: SMR = standardized mortality ratio; SIR = standardized incidence ratio; PMR = proportionate mortality ratio; SPIR = standardized proportionate incidence ratio; RR = relative risk.

^b Values in parentheses represent 90% confidence interval.

excess of cancers of the buccal mucosa or pharynx in this cohort.

In the largest industrial cohort mortality study of 26 561 workers first employed before 1966 at 10 plants in the USA (4% of cohort exposed to 2 ppm [2.4 mg/m^3]), Blair et al. (1986) observed a slight but significant (1.3-fold) excess of deaths due to lung cancer among the subcohort of white male industrial workers with 20 years since first exposure. However, results of a number of follow-up studies within this industrial group have provided little additional evidence of exposure–response (i.e., cumulative, average, peak, duration, intensity), except in the presence of other substances (Blair et al., 1986, 1990a; Marsh et al., 1992, 1996; Blair & Stewart, 1994; Callas et al., 1996).

Meta-analyses of data from epidemiological studies published between 1975 and 1991 were conducted by Blair et al. (1990b) and Partanen (1993). Blair et al. (1990b) indicated that the cumulative relative risk of nasal cancer was not significantly increased among those with lower (RR = 0.8) or higher (RR = 1.1) exposure to formaldehyde, while Partanen (1993) reported that the cumulative relative risk of sinonasal cancer among those with substantial exposure to formaldehyde was significantly elevated (i.e., RR = 1.75). In both meta-analyses, there was a significantly increased cumulative relative risk (ranging from 2.1 to 2.74) of nasopharyngeal cancer among those in the highest category of exposure to formaldehyde; in the lower or low-medium exposure categories, the cumulative relative risks for nasopharyngeal cancer ranged from 1.10 to 1.59 (Blair et al., 1990b; Partanen, 1993). The analysis of exposure–response in Blair et al. (1990b) and Partanen (1993) was based on three and five studies, respectively, in which increased risks of nasopharyngeal cancer had been observed.

Both meta-analyses revealed no increased risk of lung cancer among professionals having exposure to formaldehyde; however, among industrial workers, the cumulative relative risk for lung cancer was marginally (but significantly) increased for those with lower and low-medium (both RR = 1.2) exposure to formaldehyde, compared with those with higher (RR = 1.0) or substantial (RR = 1.1) exposure (Blair et al., 1990b; Partanen, 1993).

More recently, Collins et al. (1997) determined the cumulative relative risks of death due to nasal, nasopharyngeal, and lung cancer associated with potential exposure to formaldehyde, based upon a meta-analysis of data from case–control and cohort investigations published between 1975 and 1995. For nasal cancer, cumulative relative risks (designated as meta RR) were 0.3 (95% confidence interval [CI] = 0.1–0.9) and 1.8 (95% CI = 1.4–2.3), on the basis of the cohort and case–control studies, respectively. In contrast to the findings of Blair et

al. (1990b) and Partanen (1993), Collins et al. (1997) concluded that there was no evidence of increased risk of nasopharyngeal cancer associated with exposure to formaldehyde; the differing results were attributed to inclusion of additional more recent studies for which results were negative (particularly Gardner et al., 1993) and correction for under-reporting of expected numbers. The authors also considered that the previous analyses of exposure–response were questionable, focusing on only one cohort study and combining the unquantified medium/high-level exposure groups from the case–control studies with the quantified highest exposure group in the one positive cohort study. Although an analysis of exposure–response was not conducted by Collins et al. (1997), the authors felt that the case–control data should have been combined with the low-exposure cohort data. Based upon the results of the cohort investigations of industrial workers, pathologists, and embalmers, the relative risks for lung cancer were 1.1 (95% CI = 1.0–1.2), 0.5 (95% CI = 0.4–0.6), and 1.0 (95% CI = 0.9–1.1), respectively; the relative risk for lung cancer derived from the case–control studies was 0.8 (95% CI = 0.7–0.9).

9.2.2 Genotoxicity

An increased incidence of micronucleated buccal or nasal mucosal cells has been reported in some surveys of individuals occupationally exposed to formaldehyde (Ballarin et al., 1992; Suruda et al., 1993; Kitaeva et al., 1996; Titenko-Holland et al., 1996; Ying et al., 1997). Evidence of genetic effects (i.e., chromosomal aberrations, sister chromatid exchanges) in peripheral lymphocytes from individuals exposed to formaldehyde vapour has also been reported in some studies (Suskov & Sazonova, 1982; Bauchinger & Schmid, 1985; Yager et al., 1986; Dobiáš et al., 1988, 1989; Kitaeva et al., 1996), but not others (Fleig et al., 1982; Thomson et al., 1984; Vasudeva & Anand, 1996; Zhitkovich et al., 1996). Available data are consistent with a pattern of weak positive responses, with good evidence of effects at the site of first contact and equivocal evidence of systemic effects, although contribution of co-exposures cannot be precluded.

9.2.3 Respiratory irritancy and function

Symptoms of respiratory irritancy and effects on pulmonary function have been examined in studies of populations exposed to formaldehyde (and other compounds) in both the occupational and general environments.

In a number of studies of relatively small numbers of workers (38–84) in which exposure was monitored for individuals, there was a higher prevalence of symptoms, primarily of irritation of the eye and respiratory tract, in workers exposed to formaldehyde in the production of resin-embedded fibreglass (Kilburn et al., 1985a), chemi-

icals, and furniture and wood products (Alexandersson & Hedenstierna, 1988, 1989; Holmström & Wilhelmsson, 1988; Malaka & Kodama, 1990) or through employment in the funeral services industry (Holness & Nethercott, 1989), compared with various unexposed control groups. Due to the small numbers of exposed workers, however, it was not possible to meaningfully examine exposure–response in most of these investigations. In the one survey in which it was considered (Horvath et al., 1988), formaldehyde was a statistically significant predictor of symptoms of eye, nose, and throat irritation, phlegm, cough, and chest complaints. Workers in these studies were exposed to mean formaldehyde concentrations of 0.17 ppm (0.20 mg/m³) and greater.

Results of investigations of effects on pulmonary function in occupationally exposed populations are somewhat conflicting. Pre-shift reductions (considered indicative of chronic occupational exposure) of up to 12% in parameters of lung function (e.g., forced vital capacity, forced expiratory volume, forced expiratory flow rate) were reported in a number of smaller studies of chemical, furniture, and plywood workers (Alexandersson & Hedenstierna, 1988, 1989; Holmström & Wilhelmsson, 1988; Malaka & Kodama, 1990; Herbert et al., 1994). In general, these effects on lung function were small and transient over a workshift, with a cumulative effect over several years that was reversible after relatively short periods without exposure (e.g., 4 weeks); effects were more obvious in non-smokers than in smokers (Alexandersson & Hedenstierna, 1989). In the subset of these investigations in which exposure was monitored for individuals (i.e., excluding only that of Malaka & Kodama, 1990), workers were exposed to mean concentrations of formaldehyde of 0.3 ppm (0.36 mg/m³) and greater. In the only study in which it was examined, there was a dose–response relationship between exposure to formaldehyde and decrease in lung function (Alexandersson & Hedenstierna, 1989). However, evidence of diminished lung function was not observed in other studies of larger numbers of workers (84–254) exposed to formaldehyde through employment in wood product (cross-shift decreases that correlated with exposure to formaldehyde but not pre-shift) (Horvath et al., 1988) or resin (Nunn et al., 1990) manufacturing or in the funeral services industry (Holness & Nethercott, 1989). These groups of workers were exposed to mean concentrations of formaldehyde of up to >2 ppm (>2.4 mg/m³).

In a survey of residences in Minnesota, USA, prevalences of nose and throat irritation among residents were low for exposures to concentrations of formaldehyde less than 0.1 ppm (0.12 mg/m³) but considerable at levels greater than 0.3 ppm (0.36 mg/m³) (Ritchie & Lehnen, 1987). This study involved analysis of the relation between measured levels of formaldehyde and reported symptoms for nearly 2000 residents in 397 mobile and 494 conventional homes. Analyses for formaldehyde in

samples collected in two rooms on one occasion were conducted and classified as “low” (<0.1 ppm [<0.12 mg/m³]), “medium” (0.1–0.3 ppm [0.12–0.36 mg/m³]), and “high” (>0.3 ppm [>0.36 mg/m³]), based on the average value for the two samples. Each of the respondents (who were not aware of the results of the monitoring) was classified by four dependent variables for health effects (yes/no for eye irritation, nose/throat irritation, headaches, and skin rash) and four potentially explanatory variables — age, sex, smoking status, and low, medium, or high exposure to formaldehyde. In all cases, the effects of formaldehyde were substantially greater at concentrations above 0.3 ppm (0.36 mg/m³) than for levels below 0.3 ppm (0.36 mg/m³). Reports of eye irritation were most frequent, followed by nose and throat irritation, headaches, and skin rash. While proportions of the population reporting eye, nose, and throat irritation or headaches at above 0.3 ppm (0.36 mg/m³) were high (71–99%), those reporting effects at below 0.1 ppm (0.12 mg/m³) were low (1–2% for eye irritation, 0–11% for nose or throat irritation, and 2–10% for headaches). The prevalence of skin rash was between 5% and 44% for >0.3 ppm (>0.36 mg/m³) and between 0% and 3% for <0.1 ppm (<0.12 mg/m³).

There has been preliminary indication of effects on pulmonary function in children in the residential environment associated with relatively low concentrations of formaldehyde, of which further study seems warranted. Although there was no increase in symptoms (chronic cough and phlegm, wheeze, attacks of breathlessness) indicated in self-administered questionnaires, the prevalence of physician-reported chronic bronchitis or asthma in 298 children aged 6–15 years exposed to concentrations between 60 and 140 ppb (72 and 168 µg/m³) in their homes was increased, especially among those also exposed to ETS (Krzyzanowski et al., 1990). There was an association between exposure and response based on subdivision of the population into groups for which indoor concentrations were #40 ppb (#48 µg/m³), 41–60 ppb (48–72 µg/m³), and >60 ppb (>72 µg/m³), although the proportions of the population in the mid- and highest exposure group were small (<10% and <4%, respectively). Exposure to formaldehyde was characterized based on monitoring in the kitchen, the main living area, and each subject’s bedroom for two 1-week periods. There was no indication of whether respondents were blinded to the results of the monitoring when responding to the questionnaires. Levels of peak expiratory flow rates (PEFR) also decreased linearly with exposure, with the decrease at 60 ppb (72 µg/m³) equivalent to 22% of the level of PEFR in non-exposed children; this value was 10% at levels as low as 30 ppb (36 µg/m³). Effects in a larger sample of 613 adults were less evident, with no increase in symptoms or respiratory disease and small transient decrements in PEFR only in the morning and mainly in smokers, the significance of which is unclear. Results of exposure–response analyses in adults were not presented.

In a survey of 1726 occupants of homes containing UFFI and 720 residents of control homes, health questionnaires were administered and a series of objective tests of pulmonary function, nasal airway resistance, sense of smell, and nasal surface cytology conducted (Broder et al., 1988). The distributions of the age groups in this population were 80%, 10%, and 10% for 16 and over, <10, and 10–15 years, respectively; only the questionnaire was completed for children under the age of 10. Monitoring for formaldehyde was conducted in the homes of these residents during 2 successive days, one of which included the day on which the occupants were examined, in a central location, in all bedrooms, and in the yard. Upon analysis, there were increases in prevalences of symptoms primarily at values greater than 0.12 ppm (0.14 mg/m³) formaldehyde, although there was evidence of interaction between UFFI and formaldehyde associated with these effects. There were no effects on other parameters investigated, with the exception of a small increase in nasal epithelial squamous metaplasia in UFFI subjects intending to have their UFFI removed. The median concentration of formaldehyde in the UFFI homes was 0.038 ppm (0.046 mg/m³) (maximum, 0.227 ppm [0.272 mg/m³]); in the control homes, the comparable value was 0.031 ppm (0.037 mg/m³) (maximum, 0.112 ppm [0.134 mg/m³]). Notably, health complaints of residents in UFFI homes were significantly decreased after remediation, although the levels of formaldehyde were unchanged.

9.2.4 Immunological effects

Epidemiological studies on the effects of exposure to formaldehyde on the immune system have focused primarily upon allergic reactions (reviewed in Feinman, 1988; Bardana & Montanaro, 1991; Stenton & Hendrick, 1994). Case reports of systemic or localized allergic reactions have been attributed to the formaldehyde present in a wide variety of products. Formaldehyde is an irritant to the respiratory tract, and some reports have suggested that the development of bronchial asthma following inhalation of formaldehyde may be due to immunological mechanisms. The specific conditions of exposure as well as idiosyncratic characteristics among individuals are likely important factors in determining whether inhalation exposure to formaldehyde can result in adverse effects on pulmonary function mediated through immunological means. Immune effects (e.g., contact dermatitis) resulting from dermal exposure to formaldehyde have been more clearly defined. The concentration of formaldehyde likely to elicit contact dermatitis reactions in hypersensitive individuals may be as low as 30 mg/litre. Based on the results of surveys conducted in North America, less than 10% of patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde.

9.2.5 Other effects

Histopathological changes within the nasal epithelium have been examined in surveys of workers occupationally exposed to formaldehyde vapour (Berke, 1987; Edling et al., 1988; Holmström et al., 1989c; Boysen et al., 1990; Ballarin et al., 1992).

In all but one of the most limited of these investigations (Berke, 1987), the prevalence of metaplasia of the nasal epithelium was increased in populations exposed occupationally principally to formaldehyde compared with age-matched control populations; occasionally, also, dysplastic changes were reported in those exposed to formaldehyde. In the most extensive of these investigations and the only one in which there were individual estimates of exposure based on personal and area sampling (Holmström et al., 1989c), mean histological scores were increased in 70 workers principally exposed to formaldehyde (mean 0.25 ppm, standard deviation 0.13 ppm [mean 0.30 mg/m³, standard deviation 0.16 mg/m³]) compared with 36 unexposed controls. Where confounders were examined, they have not explained the effects. For example, in the most extensive study by Holmström et al. (1989c), changes were not significant in a population exposed to wood dust–formaldehyde that was also examined. Edling et al. (1988) observed no variation in mean histological score in workers exposed to both formaldehyde and wood dust compared with those exposed only to formaldehyde. In cases where it was examined, there was no relationship of histological scores with duration of exposure, although this may be attributable to the small numbers in the subgroups (Edling et al., 1988).

The available data are consistent, therefore, with the hypothesis that formaldehyde is primarily responsible for induction of these histopathological lesions in the nose. The weight of evidence of causality is weak, however, due primarily to the limited number of investigations of relatively small populations of workers that do not permit adequate investigation of, for example, exposure–response.

Based upon epidemiological studies, there is no clear evidence to indicate that maternal (Hemminki et al., 1985; John et al., 1994; Taskinen et al., 1994) or paternal (Lindbohm et al., 1991) exposure to formaldehyde is associated with an increased risk of spontaneous abortion.¹

There is little convincing evidence that formaldehyde is neurotoxic in occupationally exposed populations, although it has been implicated as the responsible agent in the development of neurobehavioural disorders such as insomnia, lack of concentration, memory loss, and mood and balance alterations, as well as loss of appetite in case reports and a series of cross-sectional surveys by the same investigators (Kilburn et al., 1985a,b, 1987, 1989; Kilburn & Warshaw, 1992; Kilburn, 1994). However, the reported effects, which included increases in self-reported symptoms (for which frequencies of behavioural, neurological, and dermatological symptoms were sometimes combined for analyses), or impacts on more objective measures of neurobehavioural function were confined primarily to histology workers. Attribution of the effects to formaldehyde in this group is complicated by co-exposures; indeed, sampling and analyses in a small number of histology laboratories confirmed the widely ranging concentrations of formaldehyde, xylene, chloroform, and toluene to which such workers were likely exposed. Further, there was no verification of the crude measures by which exposure to formaldehyde was distinguished from that to solvents, which was based on worker recall of time spent conducting various tasks.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Data on the aquatic toxicity of formaldehyde are numerous. The most sensitive aquatic effects identified were observed for marine algae. Formaldehyde concentrations of 0.1 and 1 mg/litre in water caused 40–50% mortality after 96 h in day-old zygotes of *Phyllospora comosa*, a brown marine macroalga endemic to south-eastern Australia. Total (100%) mortality resulted from exposures to 100 mg/litre for 24 h and 10 mg/litre for 96 h.

The 96-h no-observed-effect concentration (NOEC) and lowest-observed-effect concentration (LOEC) (per cent mortality not specified) of 7-day-old embryos of the same species were reported as 1 and 10 mg/litre, respectively, indicating that older organisms are more tolerant (Burrige et al., 1995a). Concentrations of 0.1, 1, and 10 mg/litre also reduced germination and growth rates of the zygotes and embryos (Burrige et al., 1995b).

Freshwater algae may be slightly more tolerant of formaldehyde, based on a cell multiplication inhibition test (Bringmann & Kühn, 1980a). The toxicity threshold (for a mean extinction of 3% less than that in controls) was 0.9 mg formaldehyde/litre (2.5 mg formalin/litre) (Bringmann & Kühn, 1980a).

Other freshwater microorganisms were similarly sensitive in analogous cell multiplication studies. A 48-h toxicity threshold (5% below average cell counts of controls) of 1.6 mg formaldehyde/litre (4.5 mg formalin/litre, 35% CH₂O w/w) was determined for the saprozoic flagellate protozoan *Chilomona paramaecium* (Bringmann et al., 1980), and a 72-h toxicity threshold (3% inhibition of cell multiplication, 25 °C) of 7.7 mg/litre (22 mg formalin/litre, 35% CH₂O w/w) was reported for the protozoan *Entosiphon sulcatum* (Bringmann & Kühn, 1980b). For bacteria, the 16-h toxicity threshold (3% inhibition of cell multiplication) was 4.9 mg formaldehyde/litre (14 mg formalin/litre, 35% CH₂O w/w) for *Pseudomonas putida* (Bringmann & Kühn, 1980a), and a 25-min EC₅₀ (light emission inhibition) of 2.5 mg formaldehyde/litre (242 µmol formalin/litre, 37% CH₂O w/w) was observed in the *Photobacterium phosphoreum* Microtox test (Chou & Que Hee, 1992).

The sensitivity of freshwater invertebrates to formaldehyde varies widely. The seed shrimp *Cypridopsis* sp. appears to be the most sensitive, with a 96-h EC₅₀ (immobility) of 0.36 mg formaldehyde/litre (1.05 µl formalin/litre, 37% CH₂O w/w). The snail *Helisoma* sp., bivalve *Corbicula* sp., freshwater prawn *Palaemonetes hadiakensis*, and backswimmer *Notonecta* sp. have 96-h EC₅₀ values (immobility, delayed response to tactile stimuli) of 32, 43, 160, and 287 µg/litre (93, 126, 465, and 835 µl formalin/litre, 37% CH₂O w/w), respectively, assuming 1 µl formalin/litre = 0.34 mg formaldehyde/litre (Bills et al., 1977). Reported 24-h LC₅₀ values for *Daphnia magna* range from 2 to 1000 mg/litre (IPCS, 1989).

The toxicity of formaldehyde for fish is also variable. The most sensitive freshwater fish were fingerlings of striped bass (*Roccus saxatilis*). Reardon & Harrell (1990) reported 96-h LC₅₀ values of 1.8, 5.0, 5.7, and 4.0 mg/litre (4.96, 13.52, 15.48, and 10.84 mg formalin/litre, 37% CH₂O w/w) in water with 0, 5, 10, and 15‰ salinity, respectively. These values were calculated from nominal test concentrations using probit analyses. Salinity may have an effect on the tolerance of striped bass to formaldehyde. Although the fish had been acclimated to water with a

¹ An epidemiological study on potential reproductive effects of formaldehyde exposure in women (Taskinen et al., 1999) was identified after the cut-off date for inclusion in the Canadian source document. Owing to the suggestion in this report that occupational exposure of women to formaldehyde may be associated with adverse effects on fertility, this area should be a priority for consideration in any subsequent review of health effects.

salinity of 10–30‰ prior to testing, they were most tolerant of formaldehyde in isosmotic medium (9–10‰). Since controls were not affected by the changes in salinity, there may be a compounded effect of chemical and environmental (e.g., salinity) interaction on fish survival. Wellborn (1969) reported a 96-h LC₅₀ of 6.7 mg/litre for striped bass under static conditions. Other short-term (3- to 96-h) LC₅₀s of between 10 and 10 000 mg/litre were reported for 19 species and three life stages of freshwater fish (US EPA, 1985; IPCS, 1989). In some studies, formaldehyde caused disruption of normal gill function (Reardon & Harrell, 1990).

The only data identified for marine fish were for the juvenile marine pompano (*Trachinotus carolinus*), with 24-, 48-, and 72-h LC₅₀ values of 28.8, 27.3, and 25.6 mg formaldehyde/litre (78.0, 73.7, and 69.1 mg formalin/litre, assumed to contain 37% CH₂O), respectively, in 30‰ salinity. Salinity (10, 20, 30‰) did not significantly affect the tolerance of fish to formaldehyde (Birdsong & Avault, 1971).

The sensitivity of amphibians to formaldehyde is similar to that of fish. The lowest 24-, 48-, and 72-h LC₅₀ values were 8.4, 8.0, and 8.0 mg/litre, respectively, for larvae of the leopard frog (*Rana pipiens*). Tadpoles of bullfrogs (*Rana catesbeiana*) appear more tolerant, with 24-, 48-, and 72-h LC₅₀ values of 20.1, 17.9, and 17.9 mg/litre, respectively. Larvae of the toad *Bufo* sp. had 72-h LC₅₀ and LC₁₀₀ values of 17.1 and 19.0 mg/litre, respectively (Helms, 1964). Mortality (13–100%) in tadpoles of the Rio Grande leopard frog (*Rana berlandieri*) was observed after 24 h in formaldehyde (9.2–30.5 mg/litre) (Carmichael, 1983). A NOEC (mortality) of 6.0 mg/litre was reported.

10.2 Terrestrial environment

The most sensitive effect for terrestrial organisms resulting from exposure to formaldehyde in air was an increase in the growth of shoots, but not of roots, of the common bean (*Phaseolus vulgaris*) after exposure to average measured concentrations of 65, 107, 199, and 365 ppb (78, 128, 239, and 438 µg/m³) in air (day: 25 °C, 40% humidity; night: 14 °C, 60% humidity) for 7 h/day, 3 days/week, for 4 weeks, beginning at the appearance of the first macroscopic floral bud, 20 days after emergence (Mutters et al., 1993). Although the authors concluded that there were no short-term harmful effects, it has been suggested that an imbalance between shoot and root growth may increase the vulnerability of plants to environmental stresses such as drought, because the root system may not be large enough to provide water and nutrients for healthy plant growth (Barker & Shimabuku, 1992). Other sensitive effects on terrestrial vegetation include a significant reduction of the pollen tube length of lily (*Lilium longiflorum*) following a 5-h exposure to 367 ppb (440 µg/m³) in air; total inhibition of pollen tube elongation occurred at 1400 ppb (1680 µg/m³) (Masaru et

al., 1976). A 5-h exposure to 700 ppb (840 µg/m³) caused mild atypical signs of injury in alfalfa (*Medicago sativa*), but no injury to spinach (*Spinacia oleracea*), beets (*Beta vulgaris*), or oats (*Avena sativa*) (Haagen-Smit et al., 1952).

Effects on plants were also investigated following exposure to formaldehyde in fog water. Seedlings of winter wheat (*Triticum aestivum*), aspen (*Populus tremuloides*), rapeseed (*Brassica rapa*), and slash pine (*Pinus elliotti*) were exposed to formaldehyde concentrations of 0, 9000, or 27 000 µg/litre in fog for 4.5 h/night, 3 nights/week, for 40 days. Based on an unspecified Henry's law constant, calculated corresponding atmospheric gas-phase formaldehyde concentrations were 0, 15, and 45 ppb (0, 18, and 54 µg/m³), respectively. In rapeseed grown in the formaldehyde fog, significant (*P* # 0.1) reductions in leaf area, leaf dry weight, stem dry weight, flower number, and number of mature siliques (seed pods that produce seed) were observed compared with control plants. The slash pine showed a significant increase in needle and stem growth. No effects were observed in the wheat or aspen at test concentrations (Barker & Shimabuku, 1992).

Formaldehyde is known to be an effective disinfectant that kills microorganisms such as bacteria, viruses, fungi, and parasites at relatively high concentrations (IPCS, 1989). Exposure to 2 ppm (2400 µg/m³) gaseous formaldehyde for 24 h killed 100% of spores from cultures of various species of *Aspergillus* and *Scopulariopsis*, as well as *Penicillium crustosum* (Dennis & Gaunt, 1974). In a fumigation study, the death rate of spores of *Bacillus globigii* increased from low to high with formaldehyde concentrations ranging from 42 000 to 330 000 ppb (50 000 to 400 000 µg/m³), respectively. Humidity (>50%) appeared to shorten the delay before death (Cross & Lach, 1990).

For terrestrial invertebrates, nematodes in peat were killed by fumigation applications of 370 g/litre formaldehyde solutions at a rate of 179 ml/m³ (66 g/m³) (Lockhart, 1972). Solutions of 1% and 5% formalin (37% formaldehyde) destroyed the eggs and affected larvae, respectively, of the cattle parasites *Ostertagia ostertagi* and *Cooperia oncophora* in liquid cow manure (Persson, 1973).

No acute or chronic toxicity data were identified for wild mammals, birds, reptiles, or terrestrial invertebrates. Effects on laboratory mammals are presented in section 8.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification

Inhalation, the likely principal route of exposure of the general population to formaldehyde, has been the focus of most studies on the effects of this substance in humans and laboratory animals. Available data on effects following ingestion of or dermal exposure to formaldehyde are limited. Since formaldehyde is water soluble, highly reactive with biological macromolecules, and rapidly metabolized, adverse effects resulting from exposure are observed primarily in those tissues or organs with which formaldehyde first comes into contact (i.e., the respiratory and aerodigestive tract, including oral and gastrointestinal mucosa, following inhalation and ingestion, respectively).

Effects following inhalation that occur primarily at the site of contact are, therefore, the principal focus of this section.

11.1.1.1 Genotoxicity

Results of epidemiological studies in occupationally exposed populations are consistent with a pattern of weak positive responses for genotoxicity, with good evidence of an effect at site of contact (e.g., micronucleated buccal or nasal mucosal cells). Evidence for distal (i.e., systemic) effects is equivocal (chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes). The contribution of co-exposures to observed effects cannot be precluded.

The results of a large number of *in vitro* assays of a variety of end-points indicate that formaldehyde is genotoxic at high concentrations in both bacterial and mammalian cells. The spectrum of mutation induced by formaldehyde *in vitro* varies among cell types and concentrations to which cells were exposed but includes both point and large-scale changes. Formaldehyde induced *in vitro* DNA-protein crosslinks, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, and gene mutations in human and rodent cells. It also induced cell transformation in rodent cells. The results of *in vivo* studies in animals are similar to those in humans, with effects at site of contact being observed (e.g., increased chromosomal anomalies in lung cells, micronuclei in the gastrointestinal tract, and sperm anomalies following inhalation or gavage to rats *in vivo*). Evidence of distal (systemic) effects is less convincing. Indeed, in the majority of studies of rats exposed to formaldehyde via inhalation, genetic effects within peripheral lymphocytes or bone marrow cells have not been observed.

Formaldehyde also induces the formation of DNA-protein crosslinks in a variety of human and rat cell types *in vitro* and in the epithelium of the nasal cavity of rats and respiratory tract of monkeys following inhalation, which may contribute to the carcinogenicity of the compound in the nasal cavity of rats through replication errors, resulting in mutation.

Overall, formaldehyde is genotoxic, with effects most likely to be observed *in vivo* in cells from tissues or organs with which the aldehyde first comes into contact.

11.1.1.2 Carcinogenicity

11.1.1.2.1 Inhalation

In case-control studies, associations between cancers of the nasal or nasopharyngeal cavities and formaldehyde exposure have been observed that fulfil, at least in part, traditional criteria of causality; significantly elevated odds ratios of an association were found for workers with the highest level or duration of exposure. It should be noted, though, that measures of exposure in these population-based investigations are rather less reliable than those in the larger, most extensive cohort studies of occupationally exposed populations; moreover, methodological limitations complicate interpretation of several of the case-control studies. Excesses of cancers of the nasal or nasopharyngeal cavities have not been observed consistently in cohort studies. Where there have been excesses, there has been little evidence of exposure-response, although the total number of observed tumours was small. In epidemiological studies of occupationally exposed populations, there has been little evidence of a causal association between exposure to formaldehyde and lung cancer. Indeed, results of studies in a rather extensive database of cohort and case-control studies do not fulfil traditional criteria of causality in this regard, such as consistency, strength, and exposure-response. Increases in mortality or incidence have not been observed consistently, and, where examined, there has consistently been no evidence of exposure-response.

Five carcinogenicity bioassays have provided consistent evidence that formaldehyde is carcinogenic in rats exposed via inhalation (Kerns et al., 1983; Sellakumar et al., 1985; Tobe et al., 1985; Monticello et al., 1996; Kamata et al., 1997). The incidence of nasal tumours was not significantly increased in mice exposed to formaldehyde by inhalation (Kerns et al., 1983). This has been attributed, at least in part, to the greater reduction in minute volume in mice than in rats exposed to formaldehyde (Chang et al., 1981; Barrow et al., 1983), resulting in lower exposures in mice than in rats (Barrow et al., 1983).

Observation of tumours at the site of contact is consistent with toxicokinetic considerations. Formaldehyde is a highly water-soluble, highly reactive gas that is locally

absorbed quickly at the site of contact. It is also rapidly metabolized, such that exposure to even high concentrations of atmospheric formaldehyde does not result in an increase in formaldehyde concentrations in the blood.

As described in section 8.7, the mechanisms by which formaldehyde induces nasal tumours in rats are not fully understood. However, it has been hypothesized that a sustained increase in epithelial cell regenerative proliferation resulting from cytotoxicity is a requisite precursor in the mode of induction of tumours. Mutation, for which the formation of DNA–protein crosslinks serves as a marker of potential, may also contribute to the carcinogenicity of the compound in the nasal cavity of rats. Studies relevant to assessment of the mode of action include a cancer bioassay (Monticello et al., 1996) in which intermediate end-points (proliferative response in various regions of the nasal epithelium) have been investigated. The relevant database also includes numerous shorter-term studies in which proliferative response and the formation of DNA–protein crosslinks in the nasal epithelium of rats and other species have been examined following exposure via regimens often similar to those in the cancer bioassays (Swenberg et al., 1983; Casanova & Heck, 1987; Heck & Casanova, 1987; Casanova et al., 1989, 1991, 1994; Monticello et al., 1989, 1991). It should be noted, though, that due to the limited data on intermediate end-points in most of the cancer bioassays, information available as a basis for direct comparison of the incidence of intermediate lesions (i.e., proliferative response as a measure of cytotoxicity and DNA–protein crosslinking) and tumours is limited to that presented in Table 8.

However, as would be expected for essential but not necessarily sufficient precursor events, cancer is not always associated with sustained cytotoxicity and regenerative proliferation (Monticello et al., 1991, 1996). Similarly, tumours have been observed only at concentrations at which increases in DNA–protein crosslinks have been observed in shorter-term studies in the same strain (Casanova & Heck, 1987; Heck & Casanova, 1987; Casanova et al., 1989, 1994).

In addition, where proliferative response (Monticello et al., 1991, 1996) and DNA–protein crosslinking (Casanova et al., 1994) have been examined in various regions of the nasal passages, sites at which there are increases are similar to those where tumours have been observed. The concentration–response relationships for DNA–protein crosslinking, cytotoxicity, proliferative response, and tumours are highly non-linear, with significant increases in all end-points being observed at concentrations of 4 ppm (4.8 mg/m³) and above (Table 8). This correlates well with the concentration at which mucociliary clearance is inhibited and glutathione-mediated metabolism saturated (i.e., 4 ppm [4.8 mg/m³]). Histological changes, increased epithelial cell prolifera-

tion, and DNA–protein crosslinking are all more closely related to the exposure concentration than to the total cumulative intake or dose of formaldehyde (Swenberg et al., 1983; Casanova et al., 1994).

While the respective roles of DNA–protein crosslinking, mutation, and cellular proliferation in the induction of tumours in the rat nose are not fully delineated, the hypothesized mode of carcinogenesis is in keeping with the growing body of evidence supporting the biological plausibility that prolonged regenerative cell proliferation can be a causal mechanism in chemical carcinogenesis. Regenerative cell proliferation following formaldehyde-induced cytotoxicity increases the number of DNA replications and thus increases the probability of a DNA–protein crosslink initiating a DNA replication error, resulting in a mutation. This proposed mode of action is consistent with the observed inhibition of DNA replication in the rat nose at elevated concentrations (Heck & Casanova, 1995) and point mutations in the p53 tumour suppressor gene in tumours from the noses of rats exposed to formaldehyde (Recio et al., 1992) as well as increased p53 expression in preneoplastic lesions (Wolf et al., 1995).

The hypothesized mode of induction of formaldehyde-induced tumours that satisfies several criteria for weight of evidence, including consistency, concordance of exposure–response relationships across intermediate end-points, and biological plausibility and coherence of the database, is likely relevant to humans, at least qualitatively. Increased cell proliferation (Monticello et al., 1989) and DNA–protein crosslink formation (Casanova et al., 1991) within epithelia of the upper respiratory tract have been observed in monkeys exposed to formaldehyde vapour. Although not sufficient in itself as a basis for inferring causality, direct evidence on histopathological lesions in the nose of humans exposed primarily to formaldehyde in the occupational environment is consistent with a qualitatively similar response of the upper respiratory tract in humans and experimental animals to formaldehyde. Increased human epithelial cell proliferation following *in situ* exposure to formaldehyde has also been observed in a model system in which rat trachea populated with human tracheobronchial epithelial cells were xenotransplanted into athymic mice (Ura et al., 1989).

Because formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance when extrapolating across species that have significantly different anatomical features of the nasal and respiratory passages and patterns of flow of inhaled air. Since humans as well as other primates are oronasal breathers, compared with rats, which are obligate nose breathers, effects associated with the inhalation of formaldehyde are likely to be observed in a larger area, including deeper parts of the respiratory tract. Indeed, in rats exposed to moderate levels of formaldehyde, histopathological

changes, increased epithelial cell proliferation, and DNA–protein crosslink formation are restricted to the nasal cavity; in formaldehyde-exposed monkeys (as surrogates for humans), on the other hand, these effects have been observed further along within the upper respiratory tract. While the epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde exposure and human cancer, the possibility of increased risk of respiratory cancers, particularly those of the upper respiratory tract, cannot be excluded on the basis of available data.

Based primarily upon data derived from laboratory studies, therefore, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans.

11.1.1.2.2 Oral exposure

Epidemiological studies of potential carcinogenic hazards associated with the ingestion of formaldehyde were not identified. Currently, there is no definitive evidence to indicate that formaldehyde is carcinogenic when administered orally to laboratory animals. However, consistent with the known reactivity of this substance with biological macromolecules in the tissue or organ of first contact, histopathological and cytogenetic changes within the aerodigestive tract, including oral and gastrointestinal mucosa, have been observed in rats administered formaldehyde orally. These observations and additional consideration of the mode of induction of tumours by formaldehyde lead to the conclusion that under certain conditions of exposure, potential carcinogenic hazard associated with the ingestion of formaldehyde cannot be eliminated.

11.1.1.3 Non-neoplastic effects

Sensory irritation of the eyes and respiratory tract by formaldehyde has been observed consistently in clinical studies and epidemiological (primarily cross-sectional) surveys in occupational and residential environments. The pattern of effects is consistent with increases in symptoms being reported at lowest concentrations, with the eye generally being most sensitive.

At concentrations higher than those generally associated with sensory irritation, generally small, reversible effects on lung function have been noted, although evidence of cumulative decrement in pulmonary function is limited.

Results are consistent with the increased prevalence of histological changes in the nasal epithelium in cross-sectional studies of workers being attributable to formaldehyde (Edling et al., 1988; Holmström et al., 1989c; Boysen et al., 1990; Ballarin et al., 1992). The criterion of

biological plausibility for weight of evidence of causality is also satisfied by the convincing evidence in monkeys (Rusch et al., 1983) and rodents of histopathological alterations (degenerative changes consistent with cytotoxicity) within the upper respiratory tract. Other than damage to the gastric epithelium observed following the acute ingestion of large amounts of formaldehyde (Kochhar et al., 1986; Nishi et al., 1988; IPCS, 1989), studies on potential changes within the aerodigestive tract, including oral and gastrointestinal mucosa, in humans following the long-term ingestion of this substance were not identified. However, histological changes within the surface epithelium of the aerodigestive tract, including oral and gastrointestinal mucosa of rats (e.g., erosions and/or ulcers, hyperkeratosis, hyperplasia, gastritis), have been observed following long-term oral exposure to formaldehyde administered in drinking-water at high concentrations (Til et al., 1989; Tobe et al., 1989).

Formaldehyde is not likely to affect reproduction or development at levels of exposure lower than those associated with adverse health effects at the site of contact. Based upon recent epidemiological studies of occupationally exposed individuals, there is no clear evidence indicating that either maternal or paternal inhalation exposure to formaldehyde is associated with an increased risk of spontaneous abortion (Hemminki et al., 1985; Lindbohm et al., 1991; John et al., 1994; Taskinen et al., 1994). In studies of laboratory animals exposed via inhalation (Saillenfait et al., 1989; Martin, 1990) or oral administration (Seidenberg & Becker, 1987; Wickramaratne, 1987), formaldehyde had no effect on reproduction or fetal development at levels of exposure less than those causing notable adverse health effects at the site of contact.

Based upon the available although limited data, exposure to formaldehyde is unlikely to be associated with suppression of the immune response. Indeed, the dermal hypersensitivity of some individuals to formaldehyde as well as the results of studies in animals indicate heightened immune responses linked to formaldehyde exposure. Information from epidemiological studies on suppression of the immune response associated with exposure to formaldehyde was not identified. Adverse effects on either cell- or humoral-mediated immune responses have not been consistently observed in studies conducted in laboratory animals (Dean et al., 1984; Adams et al., 1987; Holmström et al., 1989b; Jakab, 1992; Vargová et al., 1993). Although suggested in case reports for some individuals, no clear evidence that formaldehyde-induced asthma was attributable to immunological mechanisms has been identified. However, studies with laboratory animals have revealed that formaldehyde may enhance their sensitization to inhaled allergens (Tarkowski & Gorski, 1995; Riedel et al., 1996).

For the general population, dermal exposure to concentrations of formaldehyde in the vicinity of 1–2%

(10 000–20 000 mg/litre) is likely to cause skin irritation; however, in hypersensitive individuals, contact dermatitis can occur following exposure to formaldehyde at concentrations as low as 0.003% (30 mg/litre). In North America, less than 10% of patients presenting with contact dermatitis may be immunologically hypersensitive to formaldehyde.

11.1.2 Exposure–response analysis

The weight of evidence indicates that formaldehyde is carcinogenic only at concentrations that induce the obligatory precursor lesion of proliferative regenerative response associated with cytotoxicity, although interaction with DNA must also be taken into account. For consistency with other assessments and for ease of presentation, cancer and non-cancer effects are considered separately here, although, based on consideration of mode of action, they are inextricably linked.

11.1.2.1 Inhalation

11.1.2.1.1 Non-neoplastic effects

There are considered to be sufficient data from clinical studies and cross-sectional surveys of human populations, as well as supporting observations from experimental studies conducted with laboratory animals, to indicate that the irritant effects of formaldehyde on the eyes, nose, and throat occur at lowest concentration. Although individual sensitivity and exposure conditions such as temperature, humidity, duration, and co-exposure to other irritants are likely to influence response levels, in well conducted studies, only a very small proportion of the population experiences symptoms of irritation following exposure to #0.1 ppm (#0.12 mg/m³) formaldehyde. This is less than the levels that reduce mucociliary clearance in the anterior portion of the nasal cavity in available clinical studies in human volunteers (0.25 ppm [0.30 mg/m³]) and induce histopathological effects in the nasal epithelium in cross-sectional studies of formaldehyde-exposed workers (0.25 ppm [0.30 mg/m³]). Additional investigation of preliminary indication of effects on pulmonary function in children in the residential environment associated with lower concentrations of formaldehyde (40–60 ppb [48–72 µg/m³]) (Krzyzanowski et al., 1990) is warranted.

11.1.2.1.2 Carcinogenicity

There are two approaches to dose–response modelling presented here — a biologically motivated case-specific model and default, curve-fitting methodology. It is the biologically motivated case-specific model that is considered to provide the most defensible estimates of cancer risk. While this model entails simplification of cancer biology, which requires selection of a number of parameters and use of simplifying assumptions, it is considered to offer improvement over default

methodology due to incorporation of as many biological data as possible.

The preferred biologically based approach incorporates two-stage clonal growth modelling and dosimetry calculations from computational fluid dynamics modelling of formaldehyde flux in various regions of the nose and single-path modelling for the lower respiratory tract.

Sensitivity analysis conducted to determine which of the model parameters has greatest impact on risk estimates or to identify which parameters are known with the highest degree of certainty for this biologically motivated case-specific model was limited to a few parameters of the clonal growth (i.e., time delay, division rate at maximum flux into the nose of the rat, the relationship between DNA–protein crosslink concentration, and the probability of mutation per cell generation) and dosimetry (number of flux bins) components. However, output of the model is considered adequate as a basis to ensure that measures taken to prevent sensory irritation¹ in human populations are sufficiently protective with respect to carcinogenic potential.

The outcome of the biologically motivated dose–response model is compared with that derived based on empirical default methodology for estimation of tumorigenic concentrations in the experimental range (Health Canada, 1998). Moreover, in view of the clear emphasis herein and preference for the biologically motivated case-specific model, there has been no attempt to incorporate more of the biological data in the calculation of tumorigenic concentrations by default methodology (e.g., dose and time dependence to derive an empirical dose metric for rats).

1) Biologically motivated case-specific model

There is indisputable evidence that formaldehyde is carcinogenic in rats following inhalation, with the carcinogenic response being limited to the site of contact (e.g., the nasal passages of rodents). While the mechanism of action is not well understood, based primarily upon data derived from laboratory studies, regenerative proliferation associated with cytotoxicity appears to be an obligatory intermediate step in the induction of cancer by formaldehyde. Interaction with genetic material, the potential for which is indicated by DNA–protein crosslinking, likely also contributes, although the probability of mutation resulting from DNA–protein crosslinking is unknown.

However, since formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance in

¹ Occurs at lower concentrations than effects on mucociliary clearance or histopathological damage to the nose of humans.

predicting interspecies variations in response, as a function of flux to the tissue and regional tissue susceptibility, due to the significantly different anatomical features of the nasal and respiratory passages between experimental animals and humans.

The biologically motivated case-specific model incorporates regenerative cell proliferation as a required step in the induction of tumours by formaldehyde and a contribution from mutagenicity (not defined specifically by DNA–protein crosslinking) that has greatest impact at low exposures through modelling of complex functional relationships for cancer due to actions of formaldehyde on mutation, cell replication, and exponential clonal expansion. The incorporated clonal growth modelling is identical to other biologically based, two-stage clonal growth models (also known as MVK models), incorporating information on normal growth, cell cycle time, and cells at risk (in various regions of the respiratory tract). Species variations in dosimetry are taken into account by computational fluid dynamics modelling of formaldehyde flux in various regions of the nose and a single-path model for the lower respiratory tract of humans (CIIT, 1999).

Derivation of the dose–response model and selection of various parameters are summarized in Appendix 4 and presented in greater detail in CIIT (1999). Although development of the biologically motivated case-specific model required analysis of only the nasal cavity, for humans, carcinogenic risks were based on estimates of formaldehyde dose to regions (i.e., regional flux) along the entire respiratory tract.

2) Default modelling

For comparison, a tumorigenic concentration₀₅ (TC₀₅) (i.e., the concentration associated with a 5% increase in tumour incidence over background) of 7.9 ppm (9.5 mg/m³) (95% lower confidence limit [LCL] = 6.6 ppm [7.9 mg/m³]) formaldehyde was derived from data on the incidence of nasal squamous tumours in rats exposed to this substance in the single study (i.e., Monticello et al., 1996) in which exposure–response was best characterized.¹ Information on estimation of the TC₀₅ is presented in greater detail in Appendix 5.

11.1.2.2 Oral exposure

¹ Based upon the incidence of nasal tumours in rats exposed to formaldehyde, combined from the studies conducted by Kerns et al. (1983) and Monticello et al. (1996), the concentration of formaldehyde associated with a 5% increase in tumour incidence (maximum likelihood estimate) was approximately 6.1 ppm (7.3 mg/m³) (CIIT, 1999).

Lack of evidence for the potential carcinogenicity of ingested formaldehyde precludes an analysis of exposure–response for this effect.

Data on non-neoplastic effects associated with the ingestion of formaldehyde are much more limited than for inhalation. Owing to its high reactivity, non-neoplastic effects in the tissue of first contact following ingestion (i.e., the aerodigestive tract, including oral and gastrointestinal mucosa) are more likely related to the concentration of the formaldehyde consumed, rather than to its cumulative (total) intake. Information from studies on humans is inadequate to identify putative exposure–response relationships with respect to toxicological effects associated with the long-term ingestion of formaldehyde. However, a tolerable concentration (TC) for formaldehyde in ingested products may be derived on the basis of the NOEL for the development of histological changes in the aerodigestive tract, including oral and gastrointestinal mucosa of rats, as follows:

$$\begin{aligned} \text{TC} &= \frac{260 \text{ mg/litre}}{100} \\ &= 2.6 \text{ mg/litre} \end{aligned}$$

where:

- # 260 mg/litre is the NOEL for effects (i.e., histopathological changes) in the aerodigestive tract, including oral and gastrointestinal mucosa, of rats administered formaldehyde in drinking-water for 2 years in the most comprehensive study conducted (Til et al., 1989), and
- # 100 is the uncertainty factor (×10 for interspecies variation, ×10 for intraspecies variation).²

11.1.3 Sample human health risk characterization

Characterization of human health risks associated with exposure to formaldehyde is based upon analysis of the concentrations of this substance in air and some food products, rather than estimates of total daily intake *per se*, since effects are observed primarily in the tissue of first contact and are related to the level of exposure rather than to total systemic intake.

Emphasis for the characterization of health risks associated with the inhalation of formaldehyde in the environment in the sample country (i.e., Canada) is on

² Available data are inadequate to further address toxicokinetic and toxicodynamic aspects of components of uncertainty with values derived on the basis of compound-specific data, and guidance is not explicit, currently (IPCS, 1994), on more generalized replacement of kinetic components for effects related to delivered concentration.

non-neoplastic effects that occur at lowest concentrations (i.e., sensory irritation). The adequacy of this approach to protect for potential carcinogenicity is considered in the context of the biologically motivated case-specific model described above in section 11.1.2.1.2.

In humans (as well as laboratory animals), signs of ocular and upper respiratory tract sensory irritation have been observed at exposures typically greater than 100 ppb [$120 \mu\text{g}/\text{m}^3$]. The estimated median (20–24 ppb [$24\text{--}29 \mu\text{g}/\text{m}^3$]) and mean (28–30 ppb [$34\text{--}36 \mu\text{g}/\text{m}^3$]) 24-h time-weighted average exposures to formaldehyde in air in Canada are, at most, one-third of this value. This value is also greater than the estimated time-weighted average exposure (67–78 ppb [$80\text{--}94 \mu\text{g}/\text{m}^3$]) to which 95% of the population is exposed. In some indoor locations, however, concentrations may approach the level associated with signs of eye and respiratory tract sensory irritation in humans.

Based upon the biologically motivated case-specific model, the predicted additional risk of upper respiratory tract cancer for non-smoking workers with an 80-year lifetime continuous exposure to 0.004 ppm ($0.0048 \text{ mg}/\text{m}^3$) formaldehyde and having 40 years of occupational exposure (8 h/day, 5 days/week) to 1 ppm ($1.2 \text{ mg}/\text{m}^3$) formaldehyde was 8.8×10^{-6} (CIIT, 1999). For the general population, the predicted additional risks of upper respiratory tract cancer for non-smokers, associated with an 80-year continuous exposure to levels of formaldehyde between 0.001 and 0.1 ppm (1.2 and $120 \mu\text{g}/\text{m}^3$), range from 2.3×10^{-10} to 2.7×10^{-8} , respectively (CIIT, 1999). The risks of upper respiratory tract cancer predicted by the biologically motivated case-specific model to be associated with exposure to the median, mean, and 95th percentile concentrations of formaldehyde in air in Canada are also exceedingly low (i.e., $<2.7 \times 10^{-8}$).

Available information is considered insufficient to fully characterize the exposure of individuals in Canada or elsewhere to formaldehyde in foodstuffs. However, based upon limited information, the levels of formaldehyde in drinking-water (i.e., up to $10 \mu\text{g}/\text{litre}$) appear to be more than 2 orders of magnitude less than the tolerable concentration ($2.6 \text{ mg}/\text{litre}$). Although the concentration of formaldehyde in some food products would appear to exceed the tolerable concentration, the extent of its bioavailability therein is unknown.

11.1.4 Uncertainties in the evaluation of health effects

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.

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 component accounts for much of the uncertainty in the biologically motivated case-specific model.

In order to better define the mode of action of induction of tumours, elaboration of the quantitative relationship between DNA–protein crosslinks 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.

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 3 orders of magnitude less than that for the latter.

11.2 Evaluation of environmental effects

11.2.1 Assessment end-points

Formaldehyde enters the Canadian environment mainly from natural and anthropogenic combustion sources, from industrial on-site releases, from off-gassing of formaldehyde products, and through secondary formation as a result of oxidation of anthropogenic and natural organic compounds in air. Almost all releases and formation in the ambient environment are in air, with small amounts released to water.

Given its physical/chemical properties, formaldehyde is degraded by various processes in air, with very small amounts transferring into water. When released to water or soil, formaldehyde is expected to remain primarily in the original compartment of release, where it undergoes various biological and physical degradation processes. Formaldehyde is not bioaccumulative or persistent in any compartment of the environment.

Based on the sources and fate of formaldehyde in the ambient environment, biota are expected to be exposed to formaldehyde primarily in air and, to a lesser extent, in water. Little exposure of soil or benthic organisms is expected. While formaldehyde occurs naturally in plants and animals, it is readily metabolized and does not bioaccumulate in organisms. Therefore, the focus of the environmental risk characterization will be on terrestrial and aquatic organisms exposed directly to ambient formaldehyde in air and water.

11.2.1.1 Aquatic end-points

Data on aquatic toxicity are available for a variety of algae, microorganisms, invertebrates, fish, and amphibians (section 10.1). Identified sensitive end-points include effects on the development and survival of algae and invertebrates (Bills et al., 1977; Bringmann & Kühn, 1980a; BurrIDGE et al., 1995a,b), inhibition of cell multiplication in protozoa (Bringmann & Kühn, 1980a), immobilization of crustaceans (Bills et al., 1977), and mortality in fish (Reardon & Harrell, 1990).

Algae are primary producers in aquatic systems, forming the base of the aquatic food-chain, while zooplankton, including protozoans and crustaceans, are consumed by many species of invertebrates and vertebrates. Fish are consumers in aquatic communities and themselves feed piscivorous fish, birds, and mammals.

11.2.1.2 Terrestrial end-points

Data on terrestrial toxicity are available for a variety of microorganisms, plants, and invertebrates (section 10.2), as well as from mammalian toxicology studies (section 8). The most sensitive identified end-points include primarily effects on the growth and development of plants (Haagen-Smit et al., 1952; Barker & Shimabuku, 1992; Mutters et al., 1993).

Bacteria and fungi are ubiquitous in terrestrial ecosystems and, as saprophytes, are essential for nutrient cycling. Terrestrial plants are primary producers, provide food and cover for animals, and provide soil cover to reduce erosion and moisture loss. Invertebrates are an important component of the terrestrial ecosystem, consuming both plant and animal matter while serving as forage for other animals. Vertebrate wildlife species are key consumers in most terrestrial ecosystems.

Therefore, although limited, the available toxicity studies cover an array of organisms from different taxa and ecological niches and are considered adequate for an assessment of risks to terrestrial biota. The single most sensitive response for all of these end-points will be used as the critical toxicity value (CTV) for the risk characterization for terrestrial effects.

11.2.2 Sample environmental risk characterization

Results of second-tier (i.e., “conservative”) analyses are presented below, since hyperconservative analyses based on comparison of an estimated exposure value (EEV) with an estimated no-effects value (ENEV), determined by dividing a CTV by an application factor, resulted in hyperconservative quotients (EEV/ENEV) greater than 1. Additional information related to the sample environmental risk characterization is presented in Appendix 6.

11.2.2.1 Aquatic organisms

Environmental exposure to formaldehyde in water is expected to be greatest near areas of high atmospheric concentrations (where some formaldehyde can partition from air into water) and near spills or effluent outfalls. Measured concentrations are available in Canada for effluents and groundwater.

11.2.2.1.1 Effluent analysis

The highest 1-day concentration identified in an industrial effluent was 325 µg/litre (Environment Canada, 1997b). The effluent EEV was based on the conservative assumption that organisms could be living at the point of discharge.

For a conservative analysis, dilution can be considered. Hence, the hyperconservative EEV of 325 µg/litre can be divided by a generic and conservative dilution factor of 10 derived for all types of water bodies to estimate ambient concentrations of formaldehyde near outfalls. This results in a conservative effluent EEV of 32.5 µg/litre.

For aquatic organisms, a CTV of 360 µg/litre (96-h EC₅₀ for immobility in seed shrimp *Cypridopsis* sp.) (Bills et al., 1977) was selected as the most sensitive end-point from a large data set composed of toxicity studies conducted on at least 34 freshwater species of aquatic algae, microorganisms, invertebrates, fish, and amphibians. For the conservative analysis, the ENEV is derived by dividing the CTV by a factor of 10. This factor accounts for the uncertainty surrounding the extrapolation from the EC₅₀ to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. The resulting ENEV is 36 µg/litre.

The conservative quotient is calculated by dividing the EEV by the ENEV as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{32.5 \mu\text{g/litre}}{36 \mu\text{g/litre}} \\ &= 0.9 \end{aligned}$$

Since the conservative quotient is less than 1, it is unlikely that exposure to concentrations in water resulting from effluent discharge are causing adverse effects on populations of aquatic organisms in Canada.

11.2.2.1.2 Groundwater analysis

A realistic representation of groundwater quality can be achieved using a median concentration in groundwater of 100 µg/litre. The groundwater EEV was based on the conservative assumption that the groundwater could recharge directly to surface water at its full concentration. Assuming some degree of dilution similar to that of effluent in receiving water bodies, the median value can be divided by the generic and conservative dilution factor of 10 to obtain a conservative estimate of possible concentrations in the event of surface recharge. As a result, the conservative EEV for groundwater is 10 µg/litre.

The conservative quotient is calculated by dividing the EEV by the ENEV (as described above) as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{10 \mu\text{g/litre}}{36 \mu\text{g/litre}} \\ &= 0.28 \end{aligned}$$

Since the conservative quotient is less than 1, it is unlikely that concentrations of formaldehyde in groundwater are causing adverse effects on populations of aquatic organisms in Canada.

11.2.2.2 Terrestrial organisms

Environmental exposure to formaldehyde in air is expected to be greatest near sites of continuous release or formation of formaldehyde, namely in urban centres and near industrial facilities releasing formaldehyde. For a conservative analysis, the concentration selected as the EEV was 7.48 µg/m³, representing the highest 90th percentile value calculated from 354 measurements made in Toronto, Ontario, Canada, between 6 December 1989 and 18 December 1997.

For the exposure of terrestrial organisms to formaldehyde in air, the CTV is 18 µg/m³, based on the corres-

ponding amount in fog (9000 µg/litre) that affects the growth and reproduction potential of the brassica plant (*Brassica rapa*) exposed 4.5 h/night, 3 nights/week, for 40 days (Barker & Shimabuku, 1992). This value is the lowest from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial plants, microorganisms, invertebrates, and mammals exposed to air and/or fog water. Application of a factor of 2 to the CTV of 18 µg/m³ results in an ENEV for the conservative analysis of the exposure scenario for terrestrial organisms of 9 µg/m³.

The conservative quotient is calculated by dividing the EEV by the ENEV as follows:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{7.48 \mu\text{g/m}^3}{9 \mu\text{g/m}^3} \\ &= 0.83 \end{aligned}$$

Alternatively, for a conservative analysis, it may also be more realistic to use a CTV from a toxicity study involving exposure to formaldehyde in gas phase in air rather than back-calculating from exposure in fog. For the conservative analysis of the exposure of terrestrial organisms to formaldehyde in air, the CTV is 78 µg/m³, based on the lowest average concentration in air that caused a slight imbalance in the growth of shoots and roots in the common bean (*Phaseolus vulgaris*) exposed for 7 h/day, 3 days/week, for 4 weeks in air (day: 25 °C, 40% humidity; night: 14 °C, 60% humidity) (Mutters et al., 1993). This value was selected as the most sensitive endpoint from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial plants, microorganisms, invertebrates, and mammals exposed to air and/or fog water.

Dividing the CTV by a factor of 10 to account for the uncertainty surrounding the conversion of the effect concentration to a no-effect value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity, the resulting ENEV is 7.8 µg/m³. This yields the following conservative quotient:

$$\begin{aligned} \text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{7.48 \mu\text{g/m}^3}{7.8 \mu\text{g/m}^3} \\ &= 0.96 \end{aligned}$$

This quotient is very close to 1.

Given the arguments for reducing the application factor of the hyperconservative CTV for rapeseed and the even milder effects observed for the common bean plant

(Mutters et al. [1993] themselves did not conclude any ill effects from formaldehyde), the application factor can be reduced from 10 to 2 for a more realistic ENEV of $39 \mu\text{g}/\text{m}^3$. This results in a lower conservative quotient:

$$\begin{aligned}\text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{7.48 \mu\text{g}/\text{m}^3}{39 \mu\text{g}/\text{m}^3} \\ &= 0.19\end{aligned}$$

Since all three conservative quotients are less than 1, it is unlikely that formaldehyde in air causes adverse effects on terrestrial organisms in Canada.

11.2.2.3 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment. Regarding effects of formaldehyde on terrestrial and aquatic organisms, uncertainty surrounds the extrapolation from available toxicity data to potential ecosystem effects. While the toxicity data set included studies on organisms from a variety of ecological niches and taxa, there are relatively few good long-term exposure studies available. To account for these uncertainties, application factors were used in the environmental risk analysis to derive ENEVs.

For exposure in air, the measurements used in this assessment are considered acceptable because they were selected from an extensive set of recent air monitoring data of urban and other sites, including from sites at or near industrial facilities that use and release formaldehyde in Canada. These sites can also be associated with high concentrations of VOCs associated with secondary formation of formaldehyde. Thus, available data on atmospheric concentrations are considered representative of the highest concentrations likely to be encountered in air in Canada.

Only limited data are available for water, although concentrations of formaldehyde are expected to be low because of the limited releases to these media that have been identified and the limited partitioning of formaldehyde to these compartments from air. The available data on concentrations in groundwater include data from industrial sites of the users of formaldehyde. Since data are not available regarding surface recharge of the contaminated groundwater, the assessment very conservatively assumed that recharge occurred at concentrations equivalent to those measured in the groundwater with minimal dilution.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The International Agency for Research on Cancer (IARC, 1995) has classified formaldehyde in group 2A (probably carcinogenic to humans), based on limited evidence in humans and sufficient evidence in animals.

An air quality guideline of $0.1 \text{ mg}/\text{m}^3$ has been derived based upon the development of nose and throat irritation in humans; this guidance value is to be used with a 30-min averaging time (WHO, 2000). A drinking-water guideline for formaldehyde of $900 \mu\text{g}/\text{litre}$ has been derived based on a no-observed-adverse-effect level (NOAEL) of $15 \text{ mg}/\text{kg}$ body weight divided by an uncertainty factor of 100, and assuming 20% intake from water (IPCS, 1996).

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APPENDIX 1 — SOURCE DOCUMENT

Environment Canada & Health Canada (2001)

Copies of the *Canadian Environmental Protection Act* Priority Substances List assessment report (Environment Canada & Health Canada, 2001) and unpublished supporting documentation for formaldehyde may be obtained from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th floor, Place Vincent Massey
351 St. Joseph Blvd. Hull,
Quebec
Canada K1A 0H3

or

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Initial drafts of the supporting documentation and assessment report for formaldehyde were prepared by staff of Health Canada and Environment Canada. H. Hirtle, Health Canada, assisted in the preparation of the draft CICAD through inclusion of additional relevant information.

The environmental assessment was led by R. Chénier, Environment Canada, and coordinated by A. Bobra (AMBEC Environmental Consultants) on behalf of Environment Canada.

The sections of the assessment report relevant to the environmental assessment and the environmental supporting documentation were externally reviewed by A. Day (Celanese Canada Inc.), D. Mackay (University of Toronto), and P. Makar (Environment Canada).

M. Walker and J. Zielenski, Division of Biostatistics and Research Coordination, Health Canada, and D. Blakey and G. Douglas, Environmental and Occupational Toxicology Division, Health Canada, contributed to the preparation of sections on dose-response analyses for cancer and genotoxicity, respectively.

In the first stage of external review, background sections of the supporting documentation pertaining to human health were reviewed primarily to address adequacy of coverage. Written comments were provided by J. Acquavella (Monsanto Company), S. Felter (Toxicology Excellence for Risk Assessment), O. Hernandez (US EPA), R. Keefe (Imperial Oil Limited), N. Krivanek (Dupont Haskell Laboratory), J. Martin (consultant), and F. Miller (CIIT) (June 1997).

In 1996, a government-private Steering Committee was formed in the USA to develop a model for dose-response analyses for formaldehyde that takes into account as much of the biological database on formaldehyde as possible. This partnership involved primarily the CIIT and the US EPA. Toxicology Excellence for Risk Assessment, commissioned by the Formaldehyde Epidemiology, Toxicology, and Environmental Group, Inc., also participated, preparing sections of draft documentation related to hazard assessment. Health Canada joined this partnership later, contributing by organizing, in collaboration with the US EPA, an external peer review workshop and revising some sections of the draft documentation related to hazard assessment (in particular, those addressing epidemiological data).

The product of this joint effort was a draft document entitled "Formaldehyde: Hazard Characterization and Dose-Response Assessment for Carcinogenicity by the Route of Inhalation" (CIIT, 1999). This report, which was developed primarily by CIIT (with input from J. Overton, US EPA), was reviewed at an external peer review workshop of the following invitees, convened by Health Canada and the US EPA on 18-20 March 1998, in Ottawa, Ontario, Canada (Health Canada, 1998):

B. Allen, RAS Associates
M. Andersen, ICF Kaiser Engineering (Chair)
D. Blakey, Health Canada
A. Dahl, Lovelace Respiratory Research Institute
D. Gaylor, US Food and Drug Administration
J. Harkema, Michigan State University
D. Jacobson-Kram, MA BioServices
D. Krewski, Health Canada
R. Maronpot, National Institute of Environmental Health Sciences
G. Marsh, University of Pittsburgh
J. Siemiatycki, Institut Armand-Frappier
J. Ultman, Pennsylvania State University

Written comments were also provided by S. Moolgavkar (Fred Hutchinson Cancer Research Center).

Following the workshop, the report was revised to reflect comments of the external reviewers and recirculated; written comments on the subsequently revised draft were submitted by all members of the external review panel (November 1998). The final draft (dated 28 September 1999) (CIIT, 1999) was reviewed by the Chair of the workshop (M. Andersen) to ensure that comments had been adequately addressed (Andersen, 1999).

R. Vincent, Environmental Toxicology Division, Health Canada, provided comments on the assessment report. Accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard characterization and dose-response analyses were considered in written review by M. Andersen (Colorado State University), V. Feron, (TNO-Nutrition and Food Research Institute), and J. Swenberg (University of North Carolina).

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on formaldehyde 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:

- A. Aitio, International Programme on Chemical Safety, World Health Organization, Switzerland
- A. Bartholomaeus, Therapeutic Goods Administration, Health and Aged Care, Australia
- R. Benson, Drinking Water Program, US Environmental Protection Agency, USA
- R. Cary, Health and Safety Executive, United Kingdom
- R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, USA
- E. Dybing, National Institute of Public Health, Norway
- H. Gibb, National Centre for Environmental Assessment, US Environmental Protection Agency, USA
- R.C. Grafstrom, Karolinska Institute, Institute of Environmental Medicine, Sweden
- I. Gut, National Institute of Public Health, Center of Occupational Diseases, Czech Republic
- O. Harris, Agency for Toxic Substances and Disease Registry, USA
- R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany
- C. Hiremath, Environmental Carcinogenesis Division, US Environmental Protection Agency, USA
- H. Nagy, National Institute of Occupational Safety and Health, USA
- E.V. Ohanian, Office of Water, US Environmental Protection Agency, USA
- R.J. Preston, Environmental Carcinogenesis Division, US Environmental Protection Agency, USA
- J. Sekizawa, National Institute of Health Sciences, Japan
- R. Touch, Agency for Toxic Substances and Disease Registry, USA
- D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Australia
- D.C. Wolf, Environmental Carcinogenesis Division, US Environmental Protection Agency, USA
- K. Ziegler-Skylakakis, Advisory Committee for Existing Chemicals of Environmental Relevance (BUA), Germany

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Geneva, Switzerland, 8–12 January 2001

Members

- Dr A.E. Ahmed, Molecular Toxicology Laboratory, Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA
- Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom (*Chairperson*)
- Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA
- Dr S. Czerczak, Department of Scientific Information, Nofer Institute of Occupational Medicine, Lodz, Poland
- Dr S. Dobson, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom
- Dr O.M. Faroon, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA
- Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA
- Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany
- Dr A. Hirose, Division of Risk Assessment, National Institute of Health Sciences, Tokyo, Japan
- Dr P.D. Howe, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom (*Rapporteur*)
- Dr D. Lison, Industrial Toxicology and Occupational Medicine Unit, Université Catholique de Louvain, Brussels, Belgium
- Dr R. Liteplo, Existing Substances Division, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, Canada
- Dr I. Mangelsdorf, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany
- Ms M.E. Meek, Existing Substances Division, Safe Environments Program, Health Canada, Ottawa, Ontario, Canada (*Vice-Chairperson*)
- Dr S. Osterman-Golkar, Department of Molecular Genome Research, Stockholm University, Stockholm, Sweden
- Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan
- Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, El-Shatby, Alexandria, Egypt
- Dr M. Sweeney, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA
- Professor M. van den Berg, Environmental Sciences and Toxicology, Institute for Risk Assessment Sciences, University of Utrecht, Utrecht, The Netherlands

Observers

Dr W.F. ten Berge, DSM Corporate Safety and Environment, Heerlen, The Netherlands

Dr K. Ziegler-Skylakakis, Commission of the European Communities, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr Y. Hayashi, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

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

APPENDIX 4 — BIOLOGICALLY MOTIVATED CASE-SPECIFIC MODEL FOR CANCER

Derivation of the dose–response model and selection of various parameters are presented in greater detail in CIIT (1999); only a brief summary is provided here. The clonal growth component is identical to other biologically based, two-stage clonal growth models (Figure A-1) (also known as MVK models), incorporating information on normal growth, cell cycle time, and cells at risk (in various regions of the respiratory tract).

Formaldehyde is assumed to act as a direct mutagen, with the effect considered proportional to the estimated tissue concentration of DNA–protein crosslinks. The concentration–response curve for DNA–protein crosslink formation is linear at low exposure concentrations and increases in a greater than linear manner at high concentrations, similar to those administered in the rodent carcinogenicity bioassays. For cytotoxicity and subsequent regenerative cellular proliferation associated with exposure to formaldehyde, the non-linear, disproportionate increase in response at higher concentrations is incorporated. Values for parameters related to the effects of formaldehyde exposure upon the mutagenic (i.e., DNA–protein crosslink formation) and proliferative response (i.e., regenerative cell proliferation resulting from formaldehyde-induced cytotoxicity) were derived from a two-stage clonal growth model developed for rats (Figure A-2), which describes the formation of nasal tumours in animals exposed to formaldehyde.

Species-specific dosimetry within various regions of the respiratory tract in laboratory animals and humans was also incorporated. Regional dose is a function of the amount of formaldehyde delivered by inhaled air and the absorption characteristics of the lining within various regions of the respiratory tract. The amount of formaldehyde delivered by inhaled air depends upon major airflow patterns, air-phase diffusion, and absorption at the air–lining interface. The “dose” (flux) of formaldehyde to cells depends upon the amount absorbed at the air–lining interface, mucus/tissue-phase diffusion, chemical interactions such as reactions and solubility, and clearance rates. Species differences in these factors influence the site-specific distribution of lesions.

The F344 rat and rhesus monkey nasal surface for one side of the nose and the nasal surface for both sides of the human nose were mapped at high resolution to develop three-dimensional, anatomically accurate computational fluid dynamics (CFD) models of rat, primate, and human nasal airflow and inhaled gas uptake (Kimbell et al., 1997; Kepler et al., 1998; Subramaniam et al., 1998). The approximate locations of squamous epithelium and the portion of squamous epithelium coated with mucus were mapped onto the reconstructed nasal geometry of the CFD models. These CFD models provide a means for estimating the amount of inhaled gas reaching any site along the nasal passage walls and allow the direct extrapolation of exposures associated with tissue damage from animals to humans via regional nasal uptake. Although development of the two-stage clonal growth modelling for rats required analysis of only the nasal cavity, for humans, carcinogenic risks were based on estimates of formaldehyde dose to regions (i.e., regional flux) along the entire respiratory tract.

The human clonal growth modelling (Figure A-3) predicts the additional risk of formaldehyde-induced cancer within the respiratory tract under various exposure scenarios.

Two of the parameters in the human clonal growth model — the probability of mutation per cell division and the growth advantage for preneoplastic cells, both in the absence of formaldehyde exposure — were estimated statistically by fitting

the model to human 5-year age group lung cancer incidence data for non-smokers.¹ The parameter representing the time for a malignant cell to expand clonally into a clinically detectable tumour was set at 3.5 years.

In addition to the human nasal CFD model, a typical-path, one-dimensional model (see CIIT, 1999) of formaldehyde uptake was developed for the lower respiratory tract. This latter model consisted of the tracheobronchial and pulmonary regions in which uptake was simulated for four ventilatory states, based on an ICRP (1994) activity pattern for a heavy-working adult male. Nasal uptake in the lower respiratory model was calibrated to match overall nasal uptake predicted by the human CFD model. While rodents are obligate nasal breathers, humans switch to oronasal breathing when the level of activity requires a minute ventilation of about 35 litres/min. Thus, two anatomical models for the upper respiratory tract encompassing oral and nasal breathing were developed, each of which consisted basically of a tubular geometry. For the mouth cavity, the choice of tubular geometry was consistent with Fredberg et al. (1980). The rationale for using the simple tubular geometry for the nasal airway was based primarily upon the need to remove formaldehyde from the inhaled air at the same rate as in a corresponding three-dimensional CFD simulation. However, in calculations of carcinogenic risk, the nasal airway fluxes predicted by the CFD simulations, and not those predicted by the single-path model, were used to determine upper respiratory tract fluxes.

To account for oronasal breathing, there were two simulations. In one simulation, the nasal airway model represented the proximal upper respiratory tract, while in the other simulation, the mouth cavity model was used for this region. In both simulations, the fractional airflow rate in the mouth cavity or in the nasal airway was taken into account. For each segment distal to the proximal upper respiratory tract, the doses (fluxes) of formaldehyde from both simulations were added to obtain the estimated dose for oronasal breathing. The site-specific deposition of formaldehyde along the human respiratory tract coupled with data on effects upon regional DNA-protein crosslinks and cell proliferation (derived from studies in animals) (Casanova et al., 1994; Monticello et al., 1996) were reflected in calculations of carcinogenic risks associated with the inhalation of formaldehyde in humans.

Estimates of carcinogenic risks using the human clonal growth model were developed for typical environmental exposures (i.e., continuous exposure throughout an 80-year lifetime to concentrations of formaldehyde ranging from 0.001 to 0.1 ppm [0.0012 to 0.12 mg/m³]). The human clonal growth model describes a low-dose, linear carcinogenic response for humans exposed to levels of formaldehyde of #0.1 ppm (#0.12 mg/m³), where cytotoxicity and sustained cellular regenerative proliferation do not appear to play a role in tumour induction. Indeed, the effect of formaldehyde upon regenerative cellular proliferation did not have a significant impact upon the predicted carcinogenic risks at exposures between 0.001 and 0.1 ppm (0.0012 and 0.12 mg/m³). No excess risk was predicted by the human clonal growth model in a cohort exposed to formaldehyde at a specific plant examined in two epidemiological studies (Blair et al., 1986; Marsh et al., 1996). This was consistent with the observed number of cases of respiratory tract cancer (113 observed deaths; 120 expected) in the cohort. Thus, the outcome of the model was consistent with the results of the epidemiological studies.

¹ Data on predicted risks of upper respiratory tract cancers for smokers are also presented in CIIT (1999).

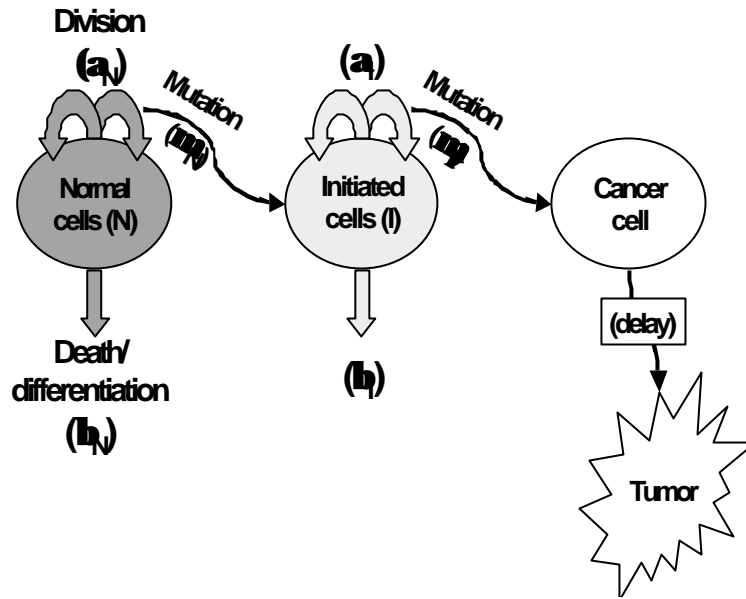


Figure A-1: Two-stage clonal growth model (reproduced from CIIT, 1999).

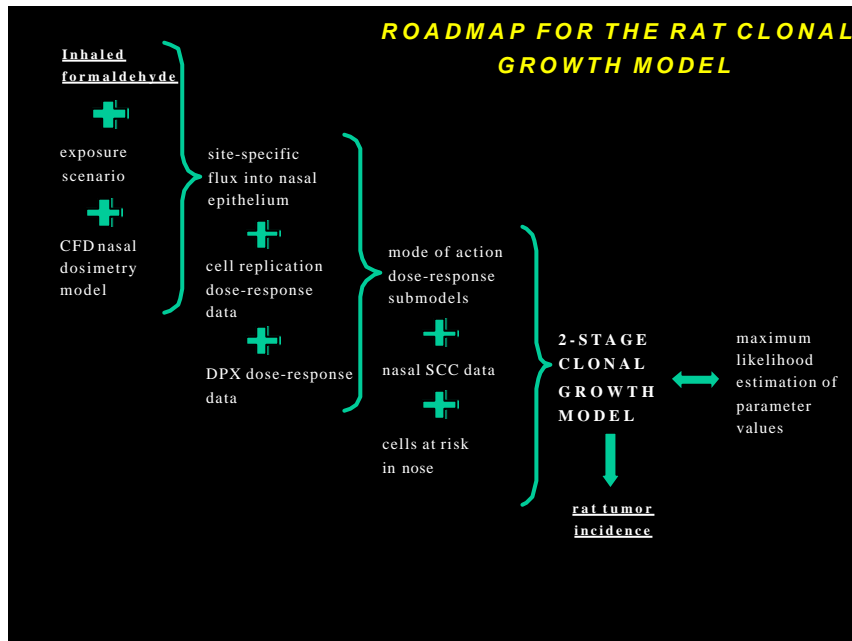
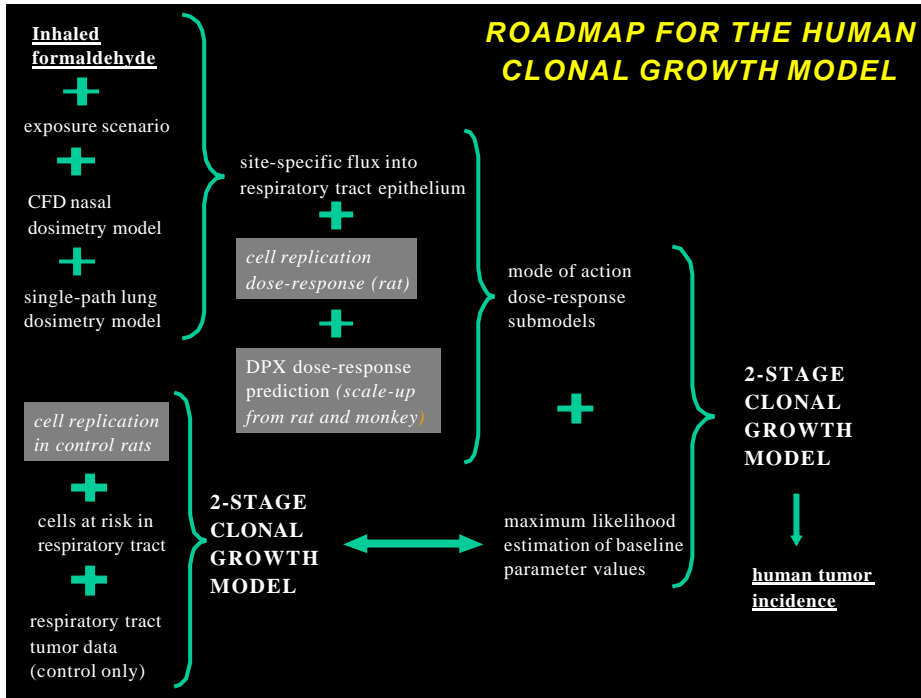


Figure A-2: Roadmap for the rat clonal growth model. CFD = computational fluid dynamics; DPX = DNA-protein crosslinking; SCC = squamous cell carcinoma (reproduced from CIIT, 1999).

Figure A-3 Road map for the human clonal growth model. Reproduced from CIIT 1999.



APPENDIX 5 — ESTIMATION OF TUMORIGENIC CONCENTRATION₀₅ (TC₀₅)

The TC₀₅ is calculated by first fitting a multistage model to the exposure–response data. The multistage model is given by

$$P(d) = 1 - e^{-q_0 - q_1 d - \dots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing a tumour at dose d , and $q_i > 0$, $i = 1, \dots, k$ are parameters to be estimated.

The model was fit using GLOBAL82 (Howe & Crump, 1982), and the TC₀₅ was calculated as the concentration C that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the three model fits. The degrees of freedom for this test are equal to k minus the number of q_i 's whose estimates are non-zero. A P -value less than 0.05 indicates a significant lack of fit. In this case, chi-square = 3.7, $df = 4$, and $P = 0.45$.

APPENDIX 6 — ADDITIONAL INFORMATION ON ENVIRONMENTAL RISK CHARACTERIZATION

Aquatic organisms

Environmental exposure to formaldehyde in water is expected to be greatest near areas of high atmospheric concentrations (where some formaldehyde can partition from air into water) and near spills or effluent outfalls. Measured concentrations are available in Canada for surface waters, effluents, and groundwater. For surface water, data are available on limited sampling at four drinking-water treatment plants in urban areas of Ontario and Alberta. Measured concentrations in effluent are available for one of the four industrial plants reporting releases of formaldehyde to water. Groundwater data are available for three industrial sites associated with spills or chronic contamination and six cemeteries in Ontario.

The highest concentration of formaldehyde reported in surface water is 9.0 µg/litre, obtained for a sample collected from the North Saskatchewan River near a treatment plant in Edmonton, Alberta (Huck et al., 1990). The highest 1-day concentration identified in an industrial effluent was 325 µg/litre (Environment Canada, 1997b). In various groundwater samples, the highest concentration of formaldehyde was 690 000 µg/litre at an industrial site (Environment Canada, 1997b). These values were used as the EEVs in the hyperconservative analysis of aquatic organisms in surface water, effluent, and groundwater, respectively. The effluent EEV was based on the conservative assumption that organisms could be living at the point of discharge. The groundwater EEV was based on the conservative assumption that the groundwater could recharge directly to surface water at its full concentration.

In the case of groundwater, the very high concentrations at one contaminated site were related to a recognized historical contamination that has since been contained and remediated (Environment Canada, 1999a). The next highest concentration reported for groundwater was for an industrial site in New Brunswick (maximum of 8200 µg/litre). It is highly unlikely that the

groundwater at a single sampling station would recharge directly to surface water. A more realistic representation of groundwater quality at the site could be achieved using the median concentration in groundwater at all sampling stations. The median was 100 µg/litre for measurements taken at five wells at the contaminated site during 1996–1997.

For a conservative analysis, an end-point should be selected that is more appropriate than that for the CTV used in the hyperconservative analysis, which was based on toxicity to a marine alga endemic to Australia. A more meaningful value can be derived by considering toxicity to the seed shrimp *Cypridopsis* sp., a common freshwater ostracod, yielding a CTV of 360 µg/litre.

Terrestrial organisms

Environmental exposure to formaldehyde in air is expected to be greatest near sites of continuous release or formation of formaldehyde, namely in urban centres and near industrial facilities releasing formaldehyde. Extensive recent data for concentrations in air are available for 27 sites, covering a range of industrial, urban, suburban, rural, and remote locations in Canada.

For a conservative analysis, a realistic estimate of long-term terrestrial exposure would be the highest of 90th percentile values calculated for each monitored site. A highest 90th percentile value is still representative of high-end concentrations at the site of greatest concern, yet it also excludes unusually high measurements, some of which may have been caused by rare ambient conditions or undetected analytical error. Analysis of the abundant data available shows that only once in the last 10 years were such high air concentrations measured in Canada for as long a period (1 month) as that from which the mean was selected for the hyperconservative EEV. Based on these data, the highest 90th percentile value is 7.48 µg/m³, calculated from 354 measurements made in Toronto, Ontario, between 6 December 1989 and 18 December 1997. This value will be used as the EEV for the conservative analysis of the exposure scenario for terrestrial organisms. For comparison, the 90th percentile value calculated for all 3842 National Air Pollution Surveillance programme measurements available between 1997 and 1998 is 5.50 µg/m³. The overall mean and median are 2.95 and 2.45 µg/m³, respectively.

For the exposure of terrestrial organisms to formaldehyde in air, the CTV is 18 µg/m³, based on the corresponding amount in fog (9000 µg/litre) that affects the growth and reproduction potential of the brassica plant (*Brassica rapa*) exposed 4.5 h/night, 3 nights/week, for 40 days (Barker & Shimabuku, 1992). This value is the lowest from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial plants, microorganisms, invertebrates, and mammals exposed to air and/or fog water.

According to Fletcher et al. (1990), there is remarkable agreement between field and laboratory EC₅₀ values for plant species. In a study of sensitivity to pesticides in a wide range of plants, only 3 of 20 field EC₅₀ values were 2-fold higher than laboratory EC₅₀ values, and only 3 of 20 laboratory EC₅₀ values were 2-fold higher than field EC₅₀ values. Therefore, no application factor may be necessary for laboratory to field extrapolations for plant effects. Furthermore, data indicated that extrapolations among plant species within a genus can be confidently made without uncertainty factors. When extrapolating from one genus to another within a family, an uncertainty factor of 2 captured 80% of the potential variability. Extrapolations across families within an order or across orders within a class should be discouraged, but, if necessary, factors of 15 and 300 should be used for intraorder and intraclass extrapolations, respectively, to capture 80% of the variability (Chapman et al., 1998). In the case of the Barker & Shimabuku (1992) study from which the CTV was selected, the four test species consisted of a deciduous tree

(aspen), a coniferous tree (slash pine), a grain crop (wheat), and a seed crop (rapeseed), representing diverse growth forms and morphology from four orders and two classes (monocots and dicots). In two of these, there were no adverse effects at test concentrations, while in a third species (slash pine), there was an arguably adverse increase in top growth at the lowest concentration. Other studies indicate that other acute and chronic effects begin to occur only at airborne concentrations clearly higher than for the rapeseed in fog, even in developmental stages (e.g., lily pollen LOEC of $440 \mu\text{g}/\text{m}^3$). The rapeseed seedling therefore appears to be by far the most sensitive of a variety of species tested. Given the diversity of the data set, only a minimal application factor may be required for interspecies extrapolation. Regarding the extrapolation from effect concentration to no-effect concentration, it should be noted that Barker & Shimabuku (1992) used a relatively low threshold of statistical significance ($\alpha = 0.1$), and effects on the rapeseed did not include any of the visual symptoms such as necrosis observed in other liquid- and gas-phase formaldehyde studies. This may therefore allow for a smaller application factor to be used on the CTV for rapeseed. Therefore, application of a factor of 2 to the CTV of $18 \mu\text{g}/\text{m}^3$ results in an ENEV for the conservative analysis of the exposure scenario for terrestrial organisms of $9 \mu\text{g}/\text{m}^3$.

Alternatively, for a conservative analysis, it may also be more realistic to use a CTV from a toxicity study involving exposure to formaldehyde in gas phase in air rather than back-calculating from exposure in fog. Reasons to do this include the exploratory nature of the fog study (Barker & Shimabuku, 1992) from which the hyperconservative CTV was selected. The conversion of fog water concentrations to expected air concentrations in the study could not be verified because variables (temperature, vapour pressure, water solubility, Henry's law constant) required for the conversion were not specified in the study. Reported exposure concentrations represented an estimated average based on the observed rate of degradation in the experimental system. Since formaldehyde in the fog water readily undergoes hydration and degradation, it is not certain how its properties may change its toxicity. Analysis of the terrestrial data set available indicates no other reports of studies on effects of fog or effects as sensitive as those in Barker & Shimabuku (1992). In addition, no data on concentrations of formaldehyde in fog in Canada or frequency of fog incidence in urban areas were identified to be able to support an assumption that Canadian biota are being exposed to formaldehyde under such conditions as those used in the experiment. Also, the study did not seem to take into consideration potential exposure to gas-phase formaldehyde in between exposures to formaldehyde in fog. A study of long-term exposure to formaldehyde in gas phase in air may be more realistic.

For the conservative analysis of the exposure of terrestrial organisms to formaldehyde in air, the CTV is $78 \mu\text{g}/\text{m}^3$, based on the lowest average concentration in air that caused a slight imbalance in the growth of shoots and roots in the common bean (*Phaseolus vulgaris*) exposed for 7 h/day, 3 days/week, for 4 weeks in air (day: 25°C , 40% humidity; night: 14°C , 60% humidity) (Mutters et al., 1993). This value was selected as the most sensitive end-point from a moderate data set composed of acute and chronic toxicity studies conducted on at least 18 species of terrestrial plants, microorganisms, invertebrates, and mammals exposed to air and/or fog water.

The 28-day intermittent exposure of the bean plant can be considered as long-term exposure (covering a significant portion of a life stage of the organism). Dividing the CTV by a factor of 10 to account for the uncertainty surrounding the conversion of the effect concentration to a no-effect value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity, the resulting ENEV is $7.8 \mu\text{g}/\text{m}^3$.

In considering a weight-of-evidence approach, other data similarly do not indicate the likelihood of high risks associated with atmospheric exposure. It is uncertain what the potential

ecological impacts could be for sensitive effects such as imbalance in growth of roots and shoots. Based on the toxicity data set available, it appears that plants are most sensitive during their early life stages. In Canada, sensitive early life stages of plants usually occur in the spring. Highest air concentrations of formaldehyde have generally been measured in late summer (August) (Environment Canada, 1999a), when atmospheric formaldehyde formation and photochemical smog formation are greatest. It would therefore appear that only the more tolerant adult plants would be exposed to the highest concentrations. In addition, in studies other than those used in the hyperconservative and conservative scenarios above, there has been considerably more tolerance to exposure to formaldehyde (e.g., no injury at concentrations below $840 \mu\text{g}/\text{m}^3$ for alfalfa; Haagen-Smit et al., 1952), with no effects on plants at a concentration of $44 \text{ mg}/\text{m}^3$ (Wolverton et al., 1984).

FORMALDEHYDE

0275

October 2000

CAS No: 50-00-0
RTECS No: LP8925000

Methanal
Methyl aldehyde
Methylene oxide
(cylinder)
H₂CO
Molecular mass: 30.0

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Extremely flammable.	NO open flames, NO sparks, and NO smoking.	Shut off supply; if not possible and no risk to surroundings, let the fire burn itself out; in other cases extinguish with powder, carbon dioxide.
EXPLOSION	Gas/air mixtures are explosive.	Closed system, ventilation, explosion-proof electrical equipment and lighting.	In case of fire: keep cylinder cool by spraying with water.

EXPOSURE		AVOID ALL CONTACT!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Burning sensation. Cough. Headache. Nausea. Shortness of breath.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Half-upright position. Artificial respiration if indicated. Refer for medical attention.
Skin		Cold-insulating gloves.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Lacrymation. Redness. Pain. Blurred vision.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Evacuate danger area! Consult an expert! Ventilation. Remove all ignition sources. Remove gas with fine water spray. Do NOT wash away into sewer. (Extra personal protection: complete protective clothing including self-contained breathing apparatus).	

EMERGENCY RESPONSE	STORAGE
	Fireproof. Cool.

IMPORTANT DATA

Physical State; Appearance

GAS, WITH CHARACTERISTIC ODOUR.

Physical dangers

The gas mixes well with air, explosive mixtures are formed easily.

Chemical dangers

The substance polymerizes due to warming. Reacts with oxidants.

Occupational exposure limits

TLV: 0.3 ppm; (ceiling values) (ACGIH 2000).
MAK: 0.5 ppm; 0.6 mg/m³; (ceiling values), skin, group 3 (1999)

Routes of exposure

The substance can be absorbed into the body by inhalation.

Inhalation risk

On loss of containment, a harmful concentration of this gas in the air will be reached very quickly.

Effects of short-term exposure

The substance is severely irritating to the eyes and is irritating to the respiratory tract. Inhalation of may cause lung oedema (see Notes).

Effects of long-term or repeated exposure

This substance is possibly carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: -20°C
Melting point: -92°C
Relative density (water = 1): 0.8
Solubility in water: very good

Relative vapour density (air = 1): 1.08
Flash point: Flammable Gas
Auto-ignition temperature: 430°C
Explosive limits, vol% in air: 7-73

ENVIRONMENTAL DATA

NOTES

The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation is therefore essential.
Immediate administration of an appropriate spray, by a doctor or a person authorized by him/her, should be considered.

ADDITIONAL INFORMATION

LEGAL NOTICE

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

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au formaldéhyde a été préparé conjointement par la Direction de l'Hygiène du Milieu de Santé Canada et la Direction de l'Évaluation des produits chimiques commerciaux d'Environnement Canada à partir d'une documentation rédigée simultanément dans le cadre du programme sur les substances prioritaires prévu par la *Loi canadienne sur la protection de l'environnement* (LCPE). Les études sur les substances prioritaires prescrites par la LCPE ont pour objectif d'évaluer les effets potentiels sur la santé humaine d'une exposition indirecte à celles de ces substances qui sont présentes dans l'environnement ainsi que leurs effets sur l'environnement lui-même. Le CICAD contient également des données sur l'exposition professionnelle. La présente mise au point prend en compte les données publiées jusqu'à fin décembre 1999 en ce qui concerne les effets sur l'environnement et jusqu'à janvier 1999 en ce qui concerne les effets sanitaires.¹ D'autres mises au point ont été également consultées, à savoir celles du CIRC (1981, 1995), de l'IPCS (1989), du RIVM (1992), de BIBRA Toxicology International (1994) et de l'ATSDR (1999). Des renseignements sur la nature de l'examen par des pairs et la disponibilité du document de base ainsi que les sources utilisées pour sa préparation (Environnement Canada & Santé Canada, 2001) sont donnés à l'appendice 1. Il est à noter, comme indiqué dans le document, que le modèle biologique spécifique utilisé pour l'analyse des relations exposition-réponse dans le cas du cancer a été mis au point conjointement par l'*Environmental Protection Agency* des États-Unis (EPA), Santé Canada, le *Chemical Industry Institute of Toxicology* (CIIT) et d'autres organismes. Le résultat de cet effort commun remplace l'avant-projet de CICAD qui avait été préparé antérieurement par l'*Office of Pollution Prevention and Toxics* de l'EPA, sur la base des données toxicologiques publiées avant 1992. Les informations concernant l'examen par des pairs du présent CICAD figurent à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Genève (Suisse), du 8 au 12 janvier 2001. La liste des participants à cette réunion se trouve à l'appendice 3. La fiche internationale sur la sécurité chimique du formaldéhyde (ICSC 0275), préparée

par le Programme international sur la sécurité chimique (IPCS, 2000), est également reproduite dans le présent document.

Le formaldéhyde (No CAS 50-0-0) se présente sous la forme d'un gaz incolore et très inflammable qui est vendu dans le commerce en solutions aqueuses à 30-50 % en poids. Il peut pénétrer dans l'environnement à partir de sources naturelles (notamment les feux de forêt), de diverses sources de combustion anthropogéniques comme par exemple les moteurs à combustion interne ou encore à la faveur de son utilisation sur certains sites industriels. Il peut également se former par oxydation des composés organiques naturels ou artificiels présents dans l'atmosphère. Les concentrations les plus élevées mesurées dans l'environnement se rencontrent au voisinage des sources anthropogéniques; ce sont elles qui constituent le principal sujet de préoccupation en ce qui concerne l'exposition de l'Homme et des autres êtres vivants. Dans le pays qui a servi de modèle pour l'établissement de ce CICAD (le Canada), la principale source anthropogénique directe de formaldéhyde est constituée par les véhicules à moteur. Les émissions provenant d'opérations industrielles sont beaucoup moins importantes. Le formaldéhyde est utilisé dans l'industrie, entre autres pour la production de résines et d'engrais.

Lorsque du formaldéhyde est libéré dans l'atmosphère ou qu'il y prend naissance, il se décompose en majeure partie et une infime quantité passe dans l'eau. Libéré dans l'eau, le formaldéhyde ne passe pas dans d'autres milieux avant de s'être décomposé. Il ne persiste pas dans l'environnement, mais comme il y est libéré ou s'y forme en permanence, il constitue une source d'exposition chronique à proximité des sites où il est émis ou formé.

L'évaluation du risque pour la santé humaine est centrée sur l'exposition atmosphérique, principalement du fait que l'on manque de données représentatives sur les concentrations présentes dans d'autres milieux que l'air et que les données relatives aux effets d'une ingestion restent limitées.

On dispose d'un grand nombre de données récentes sur la concentration du formaldéhyde dans l'air au voisinage de sites industriels, urbains, suburbains, ruraux ou écartés du pays qui a servi à l'établissement du CICAD (le Canada, comme on l'a vu plus haut). Les données relatives à la concentration dans l'air intérieur (plus élevée) sont moins nombreuses mais néanmoins très abondantes. Celles qui concernent la concentration dans l'eau sont plus limitées. Bien que le formaldéhyde soit un constituant naturel de diverses denrées alimentaires, la surveillance est généralement sporadique et axée sur les sources. Les données disponibles révèlent que c'est dans certains fruits et dans certains poissons de mer que la concentration du formaldéhyde d'origine naturelle est la plus élevée. Les produits alimentaires peuvent en contenir

¹ Les nouvelles données notées par les auteurs et obtenues par un dépouillement de la littérature effectué avant la réunion du Comité d'évaluation finale ont été examinées compte tenu de leur influence probable sur les conclusions essentielles de la présente évaluation, le but étant avant tout d'établir si leur prise en compte serait prioritaire lors d'une prochaine mise à jour. Les auteurs ayant estimé qu'elles apportaient des éléments d'information supplémentaires, on a ajouté des données plus récentes encore que non essentielles pour la caractérisation des dangers ou l'analyse des relations dose-réponse.

par suite de son utilisation comme bactériostatique lors de la production et de son adjonction à la nourriture pour animaux afin d'en faciliter la manutention. Le formaldéhyde et ses dérivés sont également ajoutés aux produits de consommation les plus divers afin d'en éviter la détérioration microbienne. La population générale est exposée lors de la combustion de diverses matières (par ex. lorsque l'on fume une cigarette ou que l'on cuisine) ou en raison de l'émission de formaldéhyde par certains matériaux de construction comme le contreplaqué.

Comme le formaldéhyde (qui est également un produit du métabolisme intermédiaire) est soluble dans l'eau, qu'il réagit énergiquement sur les macromolécules biologiques et qu'il est rapidement métabolisé, les effets nocifs de l'exposition s'observent surtout au niveau des organes ou des tissus avec lesquels il entre en premier en contact (par exemple, les voies respiratoires et aéro-digestives supérieures, et notamment les muqueuses buccale et gastrointestinale, respectivement après inhalation ou ingestion).

Les études cliniques et épidémiologiques mettent régulièrement en évidence une sensation d'irritation des yeux et des voies respiratoires sur les lieux de travail comme dans les zones résidentielles. Aux concentrations qui produisent généralement une sensation d'irritation, le formaldéhyde peut aussi exercer des effets ténus et réversibles sur la fonction pulmonaire.

En ce qui concerne la population générale, une exposition cutanée au formaldéhyde en solution à environ 1-2 % (10 000 - 20 000 mg/litre) est probablement susceptible de provoquer une irritation de l'épiderme; cependant, chez les sujets hypersensibles, il peut se produire une dermatite de contact à des concentrations de formaldéhyde ne dépassant pas 0,003 % ou 30 mg/litre. En Amérique du Nord, moins de 10 % des malades qui consultent pour une dermatite de contact pourraient être immunologiquement hypersensibles au formaldéhyde. Selon certains rapports médicaux, l'asthme produit par une exposition au formaldéhyde serait dû à des mécanismes immunologiques, mais cette hypothèse n'a pu être clairement démontrée. D'un autre côté, l'expérimentation animale montre que le formaldéhyde peut augmenter la sensibilisation à des allergènes inhalés.

Après inhalation, le formaldéhyde entraîne des effets dégénératifs non néoplasiques chez le singe et la souris et des tumeurs des fosses nasales chez le rat. *In vitro*, il forme des ponts ADN-protéines, provoque la rupture d'un des brins de l'ADN, des aberrations chromosomiques, des échanges entre chromatides-sœurs et des mutations géniques dans les cellules humaines et les cellules de rongeur. Du formaldéhyde administré par gavage ou inhalation à des rats a provoqué des aberrations chromosomiques dans les cellules pulmonaires et la formation de micronoyaux dans la muqueuse des voies digestives. Les résultats des études épidémiologiques effectuées sur des populations de sujets professionnelle-

ment exposés peuvent s'interpréter comme un ensemble de réactions génotoxiques positives mais faibles, avec de bonnes indications d'une action au point de contact (par ex. présence de micronoyaux dans les cellules de la muqueuse buccale et nasale). Les données relatives aux effets produits en distalité du point de contact (c'est-à-dire systémiques) sont ambiguës. Globalement, si on prend en considération les études sur l'Homme et l'animal, le formaldéhyde apparaît comme faiblement génotoxique, avec de bonnes indications d'effets aux points de contact, mais sans preuves convaincantes d'une action en distalité de ces points. Dans l'ensemble, les études épidémiologiques ne fournissent pas d'arguments solides en faveur d'un rapport de cause à effet entre l'exposition au formaldéhyde et le cancer chez l'Homme, encore que l'on ne puisse, sur la base des données disponibles, exclure la possibilité d'un risque accru de cancers des voies respiratoires, notamment des voies aériennes supérieures. Dans ces conditions et en s'appuyant principalement sur les études en laboratoire, on estime que l'inhalation de formaldéhyde dans des circonstances propres à induire une cytotoxicité et une prolifération régénérative soutenue, présente un risque de cancérogénicité pour l'Homme.

Dans sa majorité, la population générale est exposée à des concentrations de formaldéhyde inférieures à celles qui provoquent une sensation d'irritation (c'est-à-dire 0,083 ppm ou 0,1 mg/m³). Il peut cependant arriver que dans certains locaux, la concentration de formaldéhyde soit proche de celle qui provoque une sensation d'irritation oculaire et respiratoire chez l'Homme. Le risque de cancer estimé sur la base d'un modèle biologique spécifique en utilisant la valeur calculée de l'exposition de la population générale au formaldéhyde dans le pays d'origine (le Canada) d'après le scénario type retenu se révèle être excessivement faible. La méthode utilisée comporte une modélisation biphasique de la croissance clonale qui s'appuie sur des calculs de dose à partir d'un modèle hydrodynamique informatisé du flux de formaldéhyde dans les diverses régions des fosses nasales, la modélisation ne prenant en compte qu'un seul parcours dans le cas des voies respiratoires inférieures.

On dispose de données écotoxicologiques concernant des organismes terrestres et aquatiques très divers. En s'appuyant sur les concentrations maximales mesurées dans l'air, les eaux superficielles ou souterraines et les effluents dans le pays d'origine et selon le scénario type retenu pour l'exposition, ainsi que sur la valeur des concentrations à effet nul tirées des données expérimentales relatives aux organismes terrestres et aquatiques, on peut dire que le formaldéhyde n'a vraisemblablement aucun effet nocif sur les organismes terrestres ou aquatiques.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre el formaldehído, preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Sanidad del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basó en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias previstas en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. Este CICAD incluye además información sobre la exposición en el lugar de trabajo. En este examen se analizaron los datos identificados hasta el final de diciembre de 1999 (efectos ecológicos) y enero de 1999 (efectos en la salud humana).¹ También se consultaron otros exámenes, entre ellos los del CIIC (1981, 1995), IPCS (1989), RIVM (1992), BIBRA Toxicology International (1994) y ATSDR (1999). La información relativa al carácter del examen colegiado y la disponibilidad del documento original (Ministerios de Medio Ambiente y de Sanidad del Canadá, 2001) y su documentación justificativa figura en el apéndice 1. Hay que señalar, como se indica allí, que el modelo específico de casos con una base biológica para el análisis de la exposición-respuesta en relación con el cáncer incluido en este CICAD fue el resultado de una labor conjunta que contó con la participación de la Agencia para la Protección del Medio Ambiente (EPA) de los Estados Unidos, el Ministerio de Sanidad del Canadá, el Instituto de Toxicología de la Industria Química (CIIT) y otros. El producto de esta labor de colaboración rebasaba el contenido de un proyecto de CICAD sobre el formaldehído preparado previamente por la Oficina de Prevención de la Contaminación y de Sustancias Tóxicas de la EPA de los Estados Unidos, tomando como base información toxicológica sobre la salud publicada antes de 1992. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Ginebra (Suiza) del 8 al 12 de enero de 2001. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0275) para el formaldehído, preparada por el Programa Internacional de Seguridad de

las Sustancias Químicas (IPCS, 2000), también se reproduce en este documento.

El formaldehído (CAS N° 50-0-0) es un gas incoloro muy inflamable que se vende comercialmente como soluciones acuosas del 30%-50% (en peso). El formaldehído pasa al medio ambiente a partir de fuentes naturales (incluidos los incendios forestales) y de fuentes humanas directas, como la combustión de carburantes de los automóviles y de otros tipos y los usos industriales *in situ*. Hay también una formación secundaria por la oxidación de compuestos orgánicos naturales y de origen humano presentes en el aire. Las concentraciones más altas en el medio ambiente se han medido cerca de fuentes humanas; éstas son motivo de preocupación primordial para la exposición de las personas y de otra biota. Los vehículos de motor son la principal fuente directa de origen humano de formaldehído en el medio ambiente en el país de origen (Canadá). Las emisiones procedentes de procesos industriales son considerablemente menores. Entre los usos industriales del formaldehído cabe mencionar la producción de resinas y de fertilizantes.

La mayor parte del formaldehído que se libera o se forma en el aire se degrada y una cantidad muy pequeña se desplaza hacia el agua. Cuando se libera formaldehído en el agua, no se desplaza hacia ningún otro medio, sino que se degrada. El formaldehído no persiste en el medio ambiente, pero su emisión y formación continuadas dan lugar a una exposición crónica cerca de las fuentes de emisión y formación.

La evaluación con respecto a la salud humana se concentra sobre todo en la exposición al formaldehído suspendido en el aire, debido fundamentalmente a la falta de datos representativos sobre las concentraciones en otros medios distintos del aire y a la escasez de información sobre los efectos tras la ingestión.

Hay datos recientes abundantes sobre las concentraciones de formaldehído en el aire de zonas industriales, urbanas, suburbanas, rurales y remotas en el país de origen (Canadá). Los datos son más escasos, aunque siguen siendo todavía considerables, sobre las concentraciones en el aire de espacios cerrados, que son superiores. Los datos sobre las concentraciones en el agua son más limitados. Aunque el formaldehído es un componente natural de diversos productos alimenticios, su vigilancia generalmente ha sido irregular y se ha concentrado en el origen. Sobre la base de los datos disponibles, las concentraciones más altas de formaldehído de origen natural en los alimentos se observan en algunas frutas y peces marinos. El formaldehído puede estar presente también en los alimentos debido a su uso como agente bacteriostático en la producción y su incorporación a los piensos para mejorar sus características de manipulación. También se encuentran formaldehído y sus derivados en una amplia variedad de productos de consumo para protegerlos del deterioro que provoca la contaminación microbiana. La población general está expuesta también al

¹ Se ha incluido nueva información destacada por los examinadores y obtenida en una búsqueda bibliográfica realizada antes de la reunión de la Junta de Evaluación Final para señalar sus probables repercusiones en las conclusiones esenciales de esta evaluación, principalmente con objeto de establecer la prioridad para su examen en una actualización. Se ha añadido información más reciente, no esencial para la caracterización del peligro o el análisis de la exposición-respuesta, que a juicio de los examinadores aumentaba el valor informativo.

que se libera en la combustión (por ejemplo, de los cigarrillos y el cocinado) y de algunos materiales de los edificios, como los productos de madera prensada.

Debido a que el formaldehído (que también es un producto de metabolismo intermedio) es soluble en agua, muy reactivo con macromoléculas biológicas y se metaboliza con rapidez, se observan efectos adversos derivados de la exposición principalmente en los tejidos u órganos con los cuales entra primero en contacto (es decir, las vías respiratorias y el tracto aerodigestivo, en particular la mucosa oral y gastrointestinal, tras la inhalación o la ingestión, respectivamente).

En estudios clínicos y encuestas epidemiológicas realizados en entornos laborales y residenciales se ha observado de manera constante irritación sensorial de los ojos y las vías respiratorias. A concentraciones superiores a las generalmente relacionadas con la irritación sensorial, el formaldehído puede contribuir asimismo a la inducción de efectos generalmente pequeños y reversibles en la función pulmonar.

Para la población general, la exposición cutánea a concentraciones de formaldehído en solución en torno al 1%-2% (10 000-20 000 mg/l) es probable que provoque irritación cutánea; sin embargo, en personas hipersensibles puede producirse dermatitis por contacto tras la exposición a concentraciones de formaldehído de sólo el 0,003% (30 mg/l). En América del Norte, pueden ser inmunológicamente hipersensibles al formaldehído menos del 10% de los pacientes con dermatitis por contacto. Aunque en los informes de casos se ha indicado que para algunas personas el asma inducido por el formaldehído era atribuible a mecanismos inmunitarios, no hay pruebas convincentes de ello. Sin embargo, en estudios con animales de laboratorio el formaldehído ha aumentado su sensibilización a los alérgenos inhalados.

Tras su inhalación por los animales de laboratorio, el formaldehído provoca efectos degenerativos no neoplásicos en ratones y monos y tumores nasales en ratas. *In vitro*, el formaldehído indujo la formación de enlaces cruzados ADN-proteínas, fragmentación de las cadenas sencillas de ADN, aberraciones cromosómicas, intercambio de cromátides hermanas y mutaciones genéticas en células humanas y de roedores. El formaldehído administrado por inhalación o mediante sonda a ratas *in vivo* indujo anomalías cromosómicas en las células pulmonares y la formación de micronúcleos en la mucosa gastrointestinal. Los resultados de estudios epidemiológicos en poblaciones expuestas en el lugar de trabajo son compatibles con un modelo de respuesta positiva débil para la genotoxicidad, con pruebas claras de efectos en el lugar de contacto (por ejemplo, presencia de micronúcleos en las células de la mucosa bucal o nasal). Las pruebas para los efectos distales (es decir, sistémicos) son contradictorias. En conjunto, basándose en estudios tanto en animales como en personas, el formaldehído es débilmente genotóxico, con pruebas convincentes de un

efecto en el lugar de contacto, pero menos claras en lugares distales. Los estudios epidemiológicos considerados en conjunto no proporcionan pruebas contundentes de una asociación causal entre la exposición al formaldehído y el cáncer humano, aunque a la vista de los datos disponibles no se puede excluir la posibilidad de un mayor riesgo de cáncer de las vías respiratorias, en particular de las superiores. Por consiguiente, tomando como base fundamentalmente los datos obtenidos en estudios de laboratorio, se considera que la inhalación de formaldehído en condiciones que inducen citotoxicidad y proliferación regenerativa sostenida representa un peligro carcinogénico para las personas.

La mayor parte de la población general está expuesta a concentraciones de formaldehído suspendido en el aire inferiores a las asociadas con la irritación sensorial (es decir, 0,083 ppm [0,1 mg/m³]). Sin embargo, en algunos recintos cerrados las concentraciones pueden acercarse a las asociadas con la irritación sensorial de los ojos y las vías respiratorias en las personas. Los riesgos de cáncer estimados a partir de un modelo específico de casos con una base biológica para el cálculo de la exposición de la población general al formaldehído en el aire basándose en el modelo de exposición de muestra para el país de origen (Canadá) son sumamente bajos. Este sistema incorpora la elaboración de modelos de crecimiento clonal en dos fases y está respaldado por los cálculos de dosimetría obtenidos a partir de modelos informáticos de dinámica de fluidos para el flujo del formaldehído en diversas regiones de la nariz y de modelos de vía única para las vías respiratorias inferiores.

Hay datos relativos a la toxicidad en el medio ambiente para una gran variedad de organismos terrestres y acuáticos. A la vista de las concentraciones máximas medidas en el aire, las aguas superficiales, los efluentes y las aguas freáticas en el modelo de exposición de muestra del país de origen y de los valores sin efectos estimados obtenidos de datos experimentales para la biota terrestre y acuática, no es probable que el formaldehído provoque efectos adversos en los organismos terrestres.

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